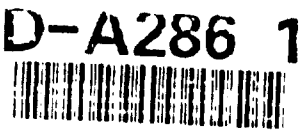


ANNUAL PROGRESS REPORT

FY-93

VOLUME II

DEPARTMENT OF CLINICAL INVESTIGATION
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, DC 20307-5001

CLINICAL INVESTIGATION PROGRAM
RCS MED-300(RI)

REPORT DATE [illegible] APRF [illegible]

DETAIL [illegible]

TITLE A Pilot Study Evaluating [illegible]
Patients with Acquired Hypogammaglobulinemia and Recurrent Chronic
Diarrhea of Undefined Etiology

KEYWORDS Immunoglobulin Hypogammaglobulinemia Diarrhea

PRINCIPAL INVESTIGATOR Engler Renata COL MC
ASSOCIATES Kikendall James COL MC Martinez Miguel MAJ MC

SERVICE Allergy-Immunology Service STATUS ngoing
APPROVAL DATE Feb 1988

FUNDING Current FY $ Previous FYs [illegible] Total [illegible]

STUDY OBJECTIVE
To develop an IgG-subclass specific ELISA for measurement of G1, G2, G3 and G4 levels in intestinal secretions, and to measure quantitative immunoglobulin levels, particularly IgG subclasses in the intestinal secretions of patients with common variable hypogammaglobulinemia and compare these with normal levels.

TECHNICAL APPROACH
Secretions previously collected under protocol #1453 normals) and those stored from medically indicated evaluations hypogammaglobulinemic patients with diarrhea) will be utilized for study An ELISA utilizing highly specific monoclonal antibodies to human G subclasses will be developed Results are to be standardized to a uniform reference and quantitated in nanograms per ml It is anticipated that additional samples will be collected on patients presenting for the problem of diarrhea and hypogammaglobulinemia as well as normals under protocol W U No 1453

PRIOR AND CURRENT PROGRESS
Samples collected by the GI Service were mislocated but were found recently for further analysis To date, total IgG IgA and IgM assays have been completed on normal intestinal secretions (N=8) and on three patients with common variable hypogammaglobulinemia (CVID) and diarrhea responsive to high dose IVIG. The IgG subclass assay is currently underway for development and will be the Fellow project for Dr Martinez The study has been hampered by the loss of all GI staff able to perform the collection of intestinal secretions under protocol W U No 1453

CONCLUSIONS
Normal subjects secrete as expected high levels of IgA into the small bowel and these studies provided information on the normal rate of secretion In addition, significant amounts of IgG were also detectable The observation that a secretory diarrhea in at CVID patients resolved within 24 hours of high dose of IVIG therapy raises the question of a regulatory process of IgG in the intestine It is also of interest which subclass might be secreted preferentially

REPORT DATE [illegible] APPROVED UNIT [illegible]

DETAIL SUMMARY SHEET

TITLE The Role of IgG Subclasses in Hymenoptera Hypersensitivity and Immunotherapy

KEYWORDS IgG subclasses hymenoptera immunotherapy

PRINCIPAL INVESTIGATOR Engler Renata [illegible]
ASSOCIATES Squire Edward LTC MC Salata Kalman PhD

SERVICE Allergy-Immunology Service STATUS Completed
APPROVAL DATE Aug 1984

FUNDING Current FY $ 0 Previous FYs $ 21,527 Total $ 21,527

STUDY OBJECTIVE
To develop a hymenoptera venom specific ELISA assay for the measurement of IgG (IgG1/2/3/4 subclasses to honey bee, wasp, yellow jacket, yellow hornet, white faced hornet), to compare the ELISA assay with the radioimmunoassay; to compare venom-specific IgG and IgG-subclass levels in patients on immunotherapy versus untreated patients with a history of anaphylaxis; and to follow patients on immunotherapy with serial venom specific G measurements.

TECHNICAL APPROACH
Patients will be enrolled during routine bee allergy evaluation days. The parameters to be evaluated include: a) skin test titration with specific venoms; b) RIA testing for venom specific IgG (VS-G) and IgE; and c) ELISA assays for venom-specific G, G4 and G1. VS-G and G4 levels will be followed sequentially in patients on venom immunotherapy (VIT) and compared to untreated patients. VS-G and G4 levels will be correlated to protection from natural sting reactions and severity level of previous sting reactions.

PRIOR AND CURRENT PROGRESS
To date, 300 patients have been enrolled. A sensitive and specific ELISA assay for measurement of VS-G1, G4 and total G was developed; both VS-G and G4 correlate well with a reputable commercial radioimmunoassay. A computerized database was utilized to track follow-up patients and correlate clinical responses to venom and VS-G/G4. Patients on VIT for over 5 years were given the option to stop therapy while VS-G/G4 levels, natural sting rates, and responses continued to be monitored. Patients who elected to continue VIT, but at increased intervals, are maintaining protective VS-G levels. VS-G and G subclass levels were followed during rush VIT in a mastocytosis patient. VS-G levels correlate to protection against anaphylaxis in first 3-4 yrs of VIT; levels decrease after 5 yrs of VIT, but G4 levels appear to remain elevated.

CONCLUSIONS
VS-G4 may be a better parameter of protection even after VIT is stopped. How long protection lasts and whether G4 levels remain elevated are questions for future study. Successful rush VIT can be carried out in patients with mastocytosis. Significant levels of VS-G are found in patients with histories of anaphylaxis and no prior VIT. Some patients have increased VS-G1, especially with serum sickness.

REPORT DATE: 11 23/9? WORK UNIT # 3336

DETAIL SUMMARY SHEET

TITLE: The Effect of Human Breast Milk Cell Supernatants on In Vitro Immunoglobulin Secretion

KEYWORDS: breast milk, immunoglobulin

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES: Carregal, Valerie CPT MC, McCormack, Emma CPT MC

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the ability of human breast milk cells in culture to continue to secrete human immunoglobulin (Ig) of all isotypes. To evaluate human breast milk cells (HBMC) supernatants (derived from cultured HBMC) in their ability to stimulate Ig secretion by peripheral blood lymphocytes PBL).

TECHNICAL APPROACH

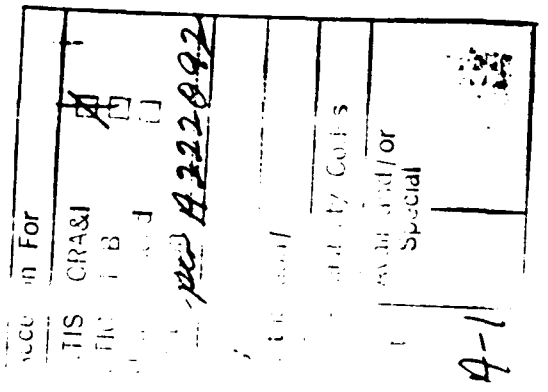
Human breast milk (HBM) is collected with a breast pump at 48 hours and 2-3 weeks after delivery. HMBC are separated and placed in culture for 7 days. Supernatants are harvested and assayed by isotype specific ELISA for quantitative Ig. HBMC supernatants are co-cultured with peripheral blood lymphocytes from normal donors for 8 days, and supernatants are again assayed for Ig production.

PRIOR AND CURRENT PROGRESS

Ten subjects have been enrolled in this study. The study has attempted to define optimum conditions for the assays, as well as adequate internal controls. Lack of technical support and increased clinical responsibities have resulted in limited progress. Dr. Miguel Martinez, a Diagnostic Laboratory Immunology fellow, will continue with the project.

CONCLUSIONS

Cells derived from HBM (colostrum) continue to release IgA over 7 days of culture even in the absence of any non-specific stimulation. Although IgA levels increase significantly in the first 24 hours, the HBM cells continue to secrete variable amounts of IgA over 7 days, even in serum free media. The role of lymphokines remains to be elucidated in this system.



REPORT DATE: 08/30/93 WORK UNIT # 3339

DETAIL SUMMARY SHEET

TITLE: Comparison of House Dust Mite Educational Programs on Selected Outcome Variables

KEYWORDS: house dust mites, D.farinae, D.pteronyssinus

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC
ASSOCIATES: Huss, Karen DNSc; Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 4,047 Total: $ 4,047

STUDY OBJECTIVE

To determine if a computerized education program about avoidance measures for house dust mite antigen leads to reduced exposure in patients with asthma. Also, under an addendum, to determine whether benzyl benzoate, when applied to carpeting in those homes in which there remained a substantial residual mite allergen burden, will actually kill mites and thereby lower the mite allergen content of these same carpets.

TECHNICAL APPROACH

This is a randomized trial. Fifty-two patients were followed with symptom diaries and home visits to determine to what extent environmental measures were taken in response to physician's recommendation. Dust was collected from each home and assayed for relevant dust mite allergens, both before and after instruction. Under an addendum, benzyl benzoate, a putative mite-killing agent, and baking soda, the control agent, will be randomly applied to home carpeting of 12 mite-allergic asthmatics. Six asthmatics will apply benzyl benzoate; six will apply baking soda. All will follow manufacturer's instructions.

PRIOR AND CURRENT PROGRESS

Though not part of the research protocol, previous findings have contributed to improved instruction of mite-allergic patients at WRAMC. Recommendations have been incorporated into existing printed materials. Such information is available for physician use when avoidance measures are being discussed with dust mite sensitive patients. Patient accrual exceeded the previous year.

CONCLUSIONS

Computer-assisted patient education improved patient compliance and outcome. However, even with this improvement, physicians must not presume that mite-allergic asthmatics will implement avoidance measures without follow-up. One of these measures, the putative acaracide benzoate, when used as directed by the manufacturer is ineffective; a longer period of application to mite-infested carpets may be crucial to effectiveness.

REPORT DATE: 08/16/93 WORK UNIT # 3340

DETAIL SUMMARY SHEET

TITLE: Analysis of Carbohydrate Epitopes on Food Allergen Proteins: A Pilot Study

KEYWORDS: carbohydrate, epitopes, allergens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Birx, Deborah MAJ MC; Engler, Renata LTC MC

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 7,478 Total: $ 7,478

STUDY OBJECTIVE
To identify and characterize carbohydrate epitopes on food allergens which react with specific IgE of patients with food allergy.

TECHNICAL APPROACH
Fluorescent enzyme linked immunosorbent assays (FELISA), sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), and immunoblotting are used to examine the role of carbohydrate epitopes in food allergy. Glycosidases, lectins, and purified saccharides are used to identify carbohydrate epitopes recognized by specific IgE from patients with food allergy.

PRIOR AND CURRENT PROGRESS
Nine subjects have been enrolled altogether; none this year. Serum IgE to foods was detected in only one subject who was extremely sensitive to foods. It has not been possible to detect IgE in sera from the other food allergic subjects. The assays used were not sensitive enough to detect food specific IgE in sera from these subjects. There have been no adverse reactions, and no one has withdrawn from the study. This study is concluded.

CONCLUSIONS
Food specific IgE assays detected antibody in only one food allergic subject who had an exquisite sensitivity to certain foods. Assays with greater sensitivity are needed for these types of studies.

REPORT DATE: 10/16/92 WORK UNIT # 3343

DETAIL SUMMARY SHEET

TITLE: Standardized Vs. Nonstandardized Allergen Products Containing Dust Mite Antigens

KEYWORDS: dust mite, potency, allergens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Berger, Teresa BSc(MT); Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 737 Total: $ 737

STUDY OBJECTIVE
To compare standardized and nonstandardized house dust mite allergen extracts for potency and allergen content.

TECHNICAL APPROACH
Fluorescent enzyme linked immunosorbent assay (FELISA) inhibition tests, sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), immunoblotting, and titrated skin prick testing are used to compare commercial allergen extracts prepared from Dermatophagoides farinae and Dermatophagoides pteronyssinus for potency and allergen content.

PRIOR AND CURRENT PROGRESS
Methods have been developed to analyze house dust mite allergens using SDS-PAGE, IEF, immunoblotting, FELISA, FELISA inhibition, and titrated house skin prick testing. A total of 14 subjects have been enrolled (5 mite allergic subjects and 9 normal subjects), with no new subjects since the last APR. There were no adverse reactions, no patients withdrew, and there were no benefits to the patients. None of the serum samples collected, so far, contain measurable IgE against mite proteins. To improve sensitivity, new monoclonal antibody reagents are being prepared. All of the products appeared, in initial studies, to have the same potency in skin tests. Immunoblots performed recently have shown quantitative and qualitative differences between extracts.

CONCLUSIONS
FDA standardization of mite extracts is based on skin test reactivity, yet the purpose of the extracts is primarily therapy, so differences in allergen content both qualitative and quantitative are important to the ultimate response of the patient. Results indicate that differences exist between extracts from different companies. Despite differences in protein content, potency, and spectrum of extract proteins and IgE reactive allergens, skin test activity is similar.

REPORT DATE: 01/21/93 WORK UNIT # 3344

DETAIL SUMMARY SHEET

TITLE: The Effect of UVB (Ultraviolet-B) Light on Immediate, Late and Delayed Hypersensitivity

KEYWORDS: ultraviolet light, skin test, allergy

PRINCIPAL INVESTIGATOR: Carpenter, Gary COL MC

SERVICE: Allergy-Immunology Service STATUS: Terminated
APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 5 Total: $ 5

STUDY OBJECTIVE

To assess the effects of ultraviolet light on immediate, late, and delayed allergen skin tests. Ultraviolet-B (UVB) has been investigated as therapy of atopic dermatitis and solar urticaria and cutaneous mastocytosis. This study may help elucidate the mechanisms in which UVB is helpful in these conditions.

TECHNICAL APPROACH

Minimal erythema dose will first be determined. The patient will then receive 1 and 2 MED and 0 MED applied to different randomized areas of the back. The patient is then skin tested at 15 minutes, 24 hours, or 72 hours, and the skin tests are read.

PRIOR AND CURRENT PROGRESS

This research protocol has been administratively terminated.

CONCLUSIONS

This research protocol has been administratively terminated.

REPORT DATE: 08/02/93 WORK UNIT # 3345

DETAIL SUMMARY SHEET

TITLE: Cross Allergenicity of Pollen Allergens from American Linden and Europen Linden

KEYWORDS: linden, pollen, cross reactivity

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service

STATUS: Completed
APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 330 Total: $ 330

STUDY OBJECTIVE

To compare the cross allogenicity of pollen from American linden and European linden trees.

TECHNICAL APPROACH

Fluorescent enzyme linked immunosorbent inhibition assays (FELISA), sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), and immunoblotting are used to compare cross allergenicity between American linden and European linden pollen.

PRIOR AND CURRENT PROGRESS

Methods have been developed to measure linden pollen protein in immunoassay techniques and in polyacrylamide gels. Little or no IgE directed against linden protein has been uncovered. Four subjects have been enrolled; no subjects have been enrolled during this reporting period. No subject has withdrawn, and there have been no serious or unexpected adverse reactions.

CONCLUSIONS

Several methods have been devised to analyze linden proteins. Little physiochemical difference was found between pollen proteins from the two species. There are substantial differences between the proteins in commercial extracts and whole pollen. Little anti-linden IgE was found in allergic's serum. A new detector may improve the sensitivity of the fluorescence assay. It is also possible that the anti-linden IgE is mostly sequestered on mast cells.

REPORT DATE: 06/16/93 WORK UNIT # 3346

DETAIL SUMMARY SHEET

TITLE: Comparison of Three Methods of Assessing Induction of Mitogen and Allergen Specific Lymphocyte Proliferation

KEYWORDS: lymphocyte, proliferation, fluorescence

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 20 Previous FYs: $ 1,630 Total: $ 1,650

STUDY OBJECTIVE

To compare three methods of measuring lymphocyte proliferation induced by dust mite allergens and lymphocyte mitogens.

TECHNICAL APPROACH

Cell counting with a Coulter counter, fluorescein release and 3H-thymidine incorporation are used to measure lymphocyte proliferation in response to allergens and mitogens. The methods are compared for sensitivity; 3H-thymidine acts as the gold standard.

PRIOR AND CURRENT PROGRESS

A method was developed to quantitate cells in culture which is based on fluorescein diacetate. This assay can be performed directly on cell cultures and requires no cell washing. The color of the plate used in the assay is important; white plates perform about 32 times better than black or clear plastic plates. Two subjects have been enrolled; one this reporting period. No one has withdrawn, and there have been no serious or unexpected adverse reactions.

CONCLUSIONS

In preliminary studies, 3H-thymidine is probably the best method for measuring lymphocyte proliferation. An assay based on cell size appears usable, and it requires little post culture manipulation. A simple fluorescent assay for quantitating cultured cells was established. A way of greatly increasing the sensitivity of 96 well plate assays was shown.

REPORT DATE: 08/16/93 WORK UNIT # 3347

DETAIL SUMMARY SHEET

TITLE: A Simple Prick Puncture End Point Titration Procedure to Evaluate the Safety of Switching from Nonstandardized to Standardized Allergen Extracts for Use in Immunotherapy

KEYWORDS: skin test, allergens, immunotherapy

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 20 Previous FYs: $ 40 Total: $ 60

STUDY OBJECTIVE
To evaluate safety and validity of a simplified skin prick puncture end-point procedure for switching between non-standardized and standardized mite extracts.

TECHNICAL APPROACH
Titrated end-point skin prick puncture tests with mite extracts will be employed.

PRIOR AND CURRENT PROGRESS
A total of 11 subjects have been enrolled in this study; 5 this past year. There have been no serious or unexpected adverse reactions, and no one has withdrawn from the study. The data has been submitted to the collaborating investigator, Dr. Seltzer, for analysis. The study has been concluded.

CONCLUSIONS
Skin prick puncture end point titration reliably measured the potency of allergen extracts of known strengths. The test is simpler and more practical in a clinic or office setting than the intradermal skin testing method for comparing potencies of allergen extracts. This test should prove useful as new standardized extracts are brought on the market.

REPORT DATE: 11/23/92 WORK UNIT # 3348

DETAIL SUMMARY SHEET

TITLE: Immunotherapy Reactions

KEYWORDS: allergy immunotherapy, venom immunotherapy, adverse reactions

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES: McCormack, Emma CPT MC; Smith, Laurie MD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Nov 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To maintain a data base of the results of an ongoing chart audit of all patients receiving immunotherapy (IT) at Walter Reed Army Medical Center since 1986; and to establish the incidence of different types of adverse reactions in relation to the following parameters: number of injections received of increasing or maintenance IT, specific extract contents, nature of all reactions, and underlying patient factors (e.g., beta blockers).

TECHNICAL APPROACH
A weekly chart review will be conducted of all patients having received IT at WRAMC Allergy Clinic. Reactions are categorized into three levels of local reactions, as well as cutaneous/systemic anaphylaxis. Data is entered into a computer data base for analysis.

PRIOR AND CURRENT PROGRESS
Chart review and data tabulation for 1989-present is ongoing. Due to variations in charting techniques of data collectors, repeating medical chart reviews began in August 1992. This has showed progress, but completion of the study is anticipated by the next annual report. Altogether, 404 medical charts have been reviewed (131 during this past year).

CONCLUSIONS
Increasing IT had significantly more systemic reactions than maintenance IT for both inhalant allergens and venom. Specific aeroallergen (AA) IT reactions were not correlated to extract type/content. Venom IT had a significantly lower rate of reaction for all three categories of local reactions (compared to AA IT, $p</=0.001$) but was not statistically different for systemic reactions.

REPORT DATE: 12/16/92 WORK UNIT # 3349

DETAIL SUMMARY SHEET

TITLE: Mitogen-Inducible T Suppressor Cell Assay by Flow Cytometry

KEYWORDS: activation, flow cytometry, suppressor

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA, Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 2,763 Total: $ 2,763

STUDY OBJECTIVE
To measure T cell suppression using a lymphocyte activation marker. To measure the suppression of mitogen stimulated lymphocytes of concanavalin A induced lymphocyte proliferation by two color flow cytometry.

TECHNICAL APPROACH
Suppression will be measured by culturing activated suppressor lymphocytes (effectors) with target lymphocytes and then measuring a parameter of activation of the targets. Lymphocyte activation will be assessed by measuring CD69 expression on the lymphocyte membrane using a monoclonal antibody. Target cells will be stained with a fluorescent vita stain, DIO, to identify them. CD69 expression will be used to assess suppression of lymphocyte activation caused by mitogen induced suppressor cells. Flow cytometry will be used to make these measurements.

PRIOR AND CURRENT PROGRESS
A two-color flow cytometric method was developed to measure mitogen induced suppressor cell function. DIO is a useful reagent for use in assays which involve mixes of more than one group of cells which must be monitored individually. CD69 in lymphocyte expression begins to appear within hours of stimulation, peaks at 18 hours, and remains elevated. Suppressor cell function was measured in a number of normal subjects. Seventeen subjects have been enrolled since this study began; there have been no adverse reactions. No new subjects have been enrolled since the last progress report. A paper is being prepared on this work, and after some additional details are addressed this study will be concluded.

CONCLUSIONS
This assay greatly improves and expands activated suppressor cell function compared to older methods. Harsh treatments of effectors and radioactive materials are avoided. The cells are allowed to function in a more natural way. This method will allow other parameters of the lymphocytes to be measured simultaneously.

REPORT DATE: 01/15/93 WORK UNIT # 3350

DETAIL SUMMARY SHEET

TITLE: Flow Cytometric Analysis of Natural Killer Cell Activity and Antibody-Dependent Cell-Mediated Cytotoxicity

KEYWORDS: flow cytometry, natural killer cells, cytotoxicity

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 48 Total: $ 48

STUDY OBJECTIVE

To measure in vitro natural killer (NK) cell activity and antibody-dependent cell cytotoxicity (ADCC) against cultured tumor cell lines using a two-color flow cytometric assay.

TECHNICAL APPROACH

The assay uses peripheral blood mononuclear cells from normal subjects as effector cells and tumor cells as target cells. Target cells are stained with a fluorescent dye, 3,3'-dioctadecyloxacarbocyanine perchlorate, to distinguish them from effector cells. Killed cells are identified using propidium iodide which stains dead cells. ADCC is measured using antibody coated cells; NK activity is measured using uncoated cells. Measurements are performed with a flow cytometer; forward light scatter, side scatter, and two colors of fluorescent light are measured.

PRIOR AND CURRENT PROGRESS

A natural killer assay has been devised with a 30 minutes incubation of the effector and target cells. This half-hour incubation time was all that was required to measure dead target cells and residual intact target cells, and has worked out well. The ADCC assay is being addressed, and a shorter incubation time will probably solve the problem of complete destruction of cells seen with a 4 hour incubation time. Also, it appears that simple vortexing of the cell pellets and chilling the incubations acts to stop the killing action, thus serving as a simple way to stop the assays. There have been no new subjects enrolled since the last progress report, for a total of seven subjects. There have been no serious and/or adverse reactions, and no one has withdrawn from the study.

CONCLUSIONS

A killer cell assay has been developed which is faster than the traditional ^{51}Cr method. This method avoids radioactive materials and allows the quality of the cells to be assessed. Progress on the ADCC method has been made. It appears that cells can be frozen and retain their killing activity. Use of the flow cytometer gives much more information than older methods of measuring killer activity.

REPORT DATE: 01 14 93 WORK UNIT # 3331

DETAIL SUMMARY SHEET

TITLE: In Vitro House Dust Mite Allergy Assays Comparison of a Monoclonal Antibody/Allergen Capture Method with a Fluorescent Allergosorbant Test

KEYWORDS: allergy, IgE, monoclonal

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 331 Total: $ 331

STUDY OBJECTIVE

To compare two in vitro methods of detecting house dust mite allergy in normal and proven allergic subjects; and to measure IgE directed against D. farinae F1 and D. pteronyssinus P1 proteins by monoclonal antibody/allergen capture and mite specific IgE by a FAST method.

TECHNICAL APPROACH

The FAST assay uses antigen coated plates in a fluorescent enzyme-linked immunosorbent assay. The capture assay employs monoclonal antibodies directed against allergen proteins. These monoclonal antibodies are used to capture allergens from a complex extract. Serum from volunteers is exposed to these immobilized allergens to detect the presence of anti-house dust mite IgE.

PRIOR AND CURRENT PROGRESS

Methods have been developed to analyze IgE directed against house dust mite allergens F1 and P1 using a fluorescent enzyme-linked immunosorbent assay and a monoclonal antibody capture method. None of the serum samples collected so far contained measurable IgE against mite proteins. To improve sensitivity, new monoclonal antibody reagents are being prepared at present. A new, more sentitive microtiter plate fluorimeter is being procured to improve the sensitivity of the tests. In addition, methods to overcome the effect of interfering mite specific IgG are being established. Two subjects were enrolled in the last reporting period, for a total of 21 subjects. There were no adverse reactions. No patients withdrew, and there was no benefit to them.

CONCLUSIONS

Two in vitro methods were used to measure IgE specific to mite allergens. In initial studies, none of the mite sensitive patients had measurable serum anti-mite IgE. Whether this is due to the sensitivity of the test or because the IgE is sequestered on mast cells is unclear. New reagents and experimental strategies are being established to improve the sensitivity of these tests.

REPORT DATE [illegible]

DETAIL SUMMARY SHEET

TITLE Use of Steroid Sparing Agents Among Asthmatics Dependent on Corticosteroids A Pilot Study

KEYWORDS: asthma, methotrexate

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC
ASSOCIATES: Lombardo, Fredric MAJ MS

SERVICE: Allergy-Immunology Service STATUS Ongoing
APPROVAL DATE Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 2,357 Total: $ 2,357

STUDY OBJECTIVE

To establish a consensus as to a rational treatment approach for severe, steroid-dependent asthma at Walter Reed Army Medical Center.

TECHNICAL APPROACH

The definition of success/failure of asthma control will be based upon seven indicators: symptoms; mini-peak flows; PRN use of bronchodilators; lung function; asthma admissions; quality of life; and willingness of physician/patient to continue treatment. This definition will be used to prospectively judge the outcome of 42 open-treatment trials among 19 steroid-dependent asthmatics, all of whom are doing poorly with conventional management. The three treatment regimens will be: 3 months of weekly methotrexate (MTX), 10-30 mg IM or PO; qid maintenance TAO, 250 mg/4 mg PO; and up to 6 months of daily Gold 3 mg PO bid.

PRIOR AND CURRENT PROGRESS

Rx:	# Trials	Successes	Failures	%
MTX	45	20	25	44
TAO	12	4	8	33
Gold	4	1	3	25

MTX continues to be successful nearly one-half the time. When it is successful, it can be withdrawn too soon, placing the patient at increased risk for recurrence of severe asthma. When it fails it may be continued too long, placing the patient at risk for side effects without likelihood of benefit.

CONCLUSIONS

Used sucessfully, benefit with methotrexate is evident within 3 months. How beneficial a new steroid sparing regime may be should also be asked, as better treatment for severe asthma continues to be sorely needed.

REPORT DATE [illegible] WORK UNIT # 3353

DETAIL SUMMARY SHEET

TITLE: Contrasuppressor Cells in Allergy Immunotherapy

KEYWORDS: flow cytometry, contrasuppressor, immunotherapy

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Mar 19

FUNDING: Current FY: $ 0 Previous FYs: $ 530 Total: $ 530

STUDY OBJECTIVE
To measure contrasuppressor T cells in individuals with multiple allergies who are on high and low dose immunotherapy with allergen extracts. Measurements will also be performed on cells from normal and untreated allergic subjects.

TECHNICAL APPROACH
Flow cytometry will be used to measure fluorescently labeled V. villosa lectin to lymphocytes.

PRIOR AND CURRENT PROGRESS
In preliminary studies using cells on hand, lectin bound to all lymphocytes. A new two-step immunostaining method using a FACScan flow cytometer is being considered to improve resolution. A different flow cytometer and a different technique will be used this FY in an attempt to visualize two cell populations. No subjects have been enrolled in this reporting period, and none have been enrolled in the study. No adverse reactions have occurred; no subjects have withdrawn.

CONCLUSIONS
Reports in the literature describe a small population of lymphocytes, contrasuppressors, which bind V. villosa lectin. In preliminary studies it was found that FITC-labeled lectin bound to all lymphocytes. Whether this binding is simply high background is unclear at present.

REPORT DATE: 04/15/93 WORK UNIT # 3354

DETAIL SUMMARY SHEET

TITLE: Two Way Mixed Lymphocyte Culture: Analysis by Two Color Flow Cytometry

KEYWORDS: MLC, flow cytometry, DIO

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 4,403 Total: $ 4,403

STUDY OBJECTIVE
To devise a two-color, simultaneous, two-way mix lymphocyte culture assay.

TECHNICAL APPROACH
Flow cytometry will be used to measure lymphocyte activation in two-way mixed lymphocyte cultures. Cell surface expression of CD69 will be used as a measure of lymphocyte activation. A fluorescent vital stain, 3,3'-dioctadecyloxacarbocyanine perchlorate, will be used to differentiate the cell populations.

PRIOR AND CURRENT PROGRESS
A flow cytometric MLC assay has been devised. Little expression of CD59 or transferrin receptor has been seen in response to allogeneic stimulation. A lot of cell death takes place during the assay. In addition, little reaction was seen using a thymidine incorporation assay. To address these problems, this assay will be run in parallel with another investigator who has a traditional assay set up. Changes in serum made no difference to the assay. A total of 19 subjects have been enrolled (2 in the last reporting period). There have been no serious or unexpected adverse reactions, and no subjects have withdrawn.

CONCLUSIONS
An assay of the mixed lymphocyte reaction based on flow cytometry and a fluorescent vital stain has been devised. Unlike other methods, both cell populations may be analyzed simultaneously, avoiding the harshness of current methods. The cells are allowed to function in a more natural fashion, and additional analyses are possible. Technical problems still exist, but these should be resolvable. Final conclusions await completion by the end of the next reporting period.

REPORT DATE: 05/18/93 WORK UNIT # 3355

DETAIL SUMMARY SHEET

TITLE: Effect of Methotrexate on Expression of Intercellular Adhesion Molecule I in Interleukin-1 Stimulated Cultured Human Cells

KEYWORDS: methotrexate, interleukin-1, ICAM-1

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 655 Total: $ 655

STUDY OBJECTIVE
To measure the effect of methotrexate on interleukin-1 (IL-1) induced ICAM-1 expression in cultured human fibroblasts and adenocarcinoma cells.

TECHNICAL APPROACH
Expression of ICAM-1 will be measured using monoclonal antibodies, flow cytometry, and enzyme-linked immunosorbent assay.

PRIOR AND CURRENT PROGRESS
Cultured cells were incubated with IL-1 to stimulate ICAM-1 expression. In general, the cells responded well. ICAM-1 was readily detectable with monoclonal antibodies and flow cytometry. Concurrent incubation of cells with methotrexate did not affect IL-1 induced ICAM-1 expression. Antibodies against the adhesion marker VCAM have been tried and little binding was noted. This may be due to technical problems with the two-step staining process. Endotoxin, a potent stimulator of ICAM-1 expression, is a ubiquitous contaminant of chemical preparations. A preparation of methotrexate for parenteral administration which is endotoxin free will be tested. This study does not use any human subjects.

CONCLUSIONS
ICAM-1 expression on human lung epithelioid cells in culture is being measured by flow cytometry. Methotrexate does not appear to inhibit ICAM-1 expression in these cells. It is possible that endotoxin contamination may be confounding these measurments. The anti-inflammatory actions of methotrexate may not be mediated by inhibition of IL-1 induced ICAM-1 expression.

REPORT DATE: 09/15/93 WORK UNIT # 3357

DETAIL SUMMARY SHEET

TITLE: Serum and Secretory Immune Status of Patients with Chronic Sinusitis and Normals

KEYWORDS: sinusitis, immunodeficiency, mucosal immunity

PRINCIPAL INVESTIGATOR: McCormack, Emma MAJ MC
ASSOCIATES: Engler, Renata LTC(P) MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 526 Previous FYs: $ 13,444 Total: $ 13,970

STUDY OBJECTIVE
To evaluate the humoral, cellular, and mucosal immune responses of patients with chronic sinusitis in comparison with normal controls.

TECHNICAL APPROACH
Functional humoral immunity will be assessed by measuring total and antigen-specific antibody levels. Pre/post immunization with tetanus/diphtheria/H influenza type b and Pneumovax will be given. Cellular immune function will be evaluated using delayed hypersensitivity skin testing, lymphocyte phenotyping and in vitro lymphocyte functional assays; mucosal immune function will be measured by collection of nasal secretions in response to methacholine and histamine; and IgG, IgA, secretory IgA, lactoferrin, lysozyme and albumin measurements will be analyzed.

PRIOR AND CURRENT PROGRESS
To date, 41 subjects have been entered into this study; 8 new patients have been entered this past year. There have been no serious or unexpected adverse reactions. Data from previous assays have been entered into the computer data base. IL-2 and IL-4 levels in nasal secretions and saliva from a representative group of patients were measured by ELISA. The interleukins will be assayed in the remaining patient samples.

CONCLUSIONS
Study is ongoing; no conclusions have been reached at this time.

REPORT DATE: 09/15/93 WORK UNIT # 2358

DETAIL SUMMARY SHEET

TITLE: Plasma Level of Mast Cell Tryptase in Patients Undergoing Immunodiagnostic or Immunotherapy Procedures who Experience Adverse Reactions

KEYWORDS: tryptase, anaphylaxis, mast cell

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 320 Previous FYs: $ 6,362 Total: $ 6,682

STUDY OBJECTIVE
To measure tryptase levels in blood samples from patients in the Allergy/Immunology Clinic who experience local or systemic reactions in response to diagnostic or immunotherapy procedures.

TECHNICAL APPROACH
Immunoassays will be used to measure mast cell tryptase levels in blood samples from subjects who have experienced a reaction, as well as from subjects who have not had a reaction. Samples are drawn at the time of the reaction and a period of days later. The second sample acts as a baseline sample. Control subjects will have the blood samples drawn in a similar manner with a similar time period between samples.

PRIOR AND CURRENT PROGRESS
The immunoassay works well. To date, all but two samples have been negative for tryptase There have been no false positives. The assay is a very simple radioimmunoassay which works well with controls and standards One subject has been enrolled this year, for a total of 52. Subjects with a wide variety of reactions as well as control subjects have been enrolled. There have been no adverse reactions, and no subject has withdrawn from the study. The testing of samples was completed this past year. No more subjects will be enrolled. A paper describing the results is in preparation, and the study will be closed when it is completed.

CONCLUSIONS
A mast cell tryptase radioimmunoassay has been established in the laboratory. It appears that only vigorous anaphylactic reactions produce measurable levels of tryptase in the blood. This test does not appear to be of much utility in diagnosing the milder systemic allergic reactions.

REPORT DATE: 11/16/92 WORK UNIT # 3359

DETAIL SUMMARY SHEET

TITLE: Leukotriene B4 Receptor Downregulation: Flow Cytometry Analysis

KEYWORDS: leukotriene B4, flow cytometry, down regulation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa Berger BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 20 Previous FYs: $ 834 Total: $ 854

STUDY OBJECTIVE
To measure leukotriene B4 (LTB4) binding and calcium ion (CA++) release after an initial challenge with LTB4 in granulocytes from normal subjects using a flow cytometric assay.

TECHNICAL APPROACH
Two-color flow cytometry will be used with a fluorescein isothiocyanate (FITC) labeled LTB4 to measure receptor down regulation in granulocytes. A calcium indicator FLUO-3AM will be used to measure cytosolic calcium levels during stimulation.

PRIOR AND CURRENT PROGRESS
LTB4-FITC binds to granulocytes. Brief preincubation with LTB4 results in receptor down regulation. LTB4 also competitively inhibits LTB4-FITC binding. A flow cytometric assay has been developed to measure LTB4-FITC binding to granulocytes. A method to measure changes of cytosolic calcium using flow cytometry has been established. No subjects have been enrolled during this reporting period; two subjects were enrolled the first year of this study. No subject has withdrawn or had an adverse reaction. There were no benefits to patients.

CONCLUSIONS
LTB4 receptor down regulation can be measured by flow cytometry using an FITC labeled LTB4 conjugate. Brief incubation with LTB4 leads to down regulation of the LTB4 receptor. Additional experiments will be performed to confirm these results and the effects on mobilization of intracellular calcium. Final conclusions await the completion of this study.

REPORT DATE: 11/16/92 WORK UNIT # 3360

DETAIL SUMMARY SHEET

TITLE: 3,3'-Dioctadecyloxacarbocyanine (DiO) Induced Immunosuppression: Inhibition of Mitogen, Antigen and Alloantigen Stimulated CD69 Expression

KEYWORDS: carbocyanine (DIO), CD69, immunosuppression

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 632 Total: $ 632

STUDY OBJECTIVE
To measure inhibition by 3,3'-dioctadecyloxacarbocyanine perchlorate (DIO) of lymphocyte activation in lymphocytes stimulated with mitogens and antigens using an antibody directed against a lymphocyte activation marker.

TECHNICAL APPROACH
Two-color flow cytometry will be used with activation marker analysis to measure the immunosuppressive effect of 3,3'-dioctadecyloxacarbocyanine perchlorate (DIO).

PRIOR AND CURRENT PROGRESS
DIO inhibits mitogen stimulated lymphocyte activation. The assay used is very simple and rapid; an answer can be obtained in less than 24 hours. Complete and irreversible inhibition of lymphocyte activation was achieved with brief exposure to 1uM DIO. The dye does not appear to interfere with measurement of constitutively expressed cell surface antigens. Two subjects have been enrolled since the last report, for a total of 16 subjects. No subject has withdrawn or had an adverse reaction. There were no benefits to patients.

CONCLUSIONS
DIO is a lipid soluble vital stain with little or no reported toxicities and is a potent inhibitor of CD69 expression and lymphocyte activation. The mechanism of action of this agent is now known and is the subject of further investigation.

REPORT DATE: 12/08/92 WORK UNIT # 3361

DETAIL SUMMARY SHEET

TITLE: Pneumococcal Polysaccharide Vaccine: Adverse Reactions to Immunization

KEYWORDS: pneumococcal, polysaccharide, immunization

PRINCIPAL INVESTIGATOR: Polly, Shirley MAJ MC
ASSOCIATES: Engler, Renata LTC(P) MC; Davis, William MAJ MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence and prevalence of adverse reactions to primary immunization versus booster immunization with the polyvalent pneumococcal polysaccharide vaccine during the annual influenza vaccination program.

TECHNICAL APPROACH
Charts from patients who have received immunizations in the Allergy-Immunization Clinic of WRAMC were reviewed for types of vaccines received. Patients are called within 6 weeks of vaccination and questioned regarding side effects, including local and systemic reactions, treatment received/required, and duration of symptoms. Data will be entered into a data base for analysis by patient/vaccination characteristics.

PRIOR AND CURRENT PROGRESS
A total of 432 patients were enrolled in the study during the period Oct 90 - Nov 90. No additional patients have been enrolled. Because of the retrospective nature of the study, no patients have withdrawn, and no unexpected adverse reactions have been encountered. Approximately 4000 patients received immunizations during the study period. Currently, immunization data on these patients is being verified for accuracy in order to provide denominators for the analysis of the study patients.

CONCLUSIONS
A preliminary analysis of the data revealed no significant difference in incidence of side effects due to primary versus booster immunization. Complete analysis is pending completion of the data base, which requires verification of the information on patients who received immunizations during the study period but were not contacted as part of the study.

REPORT DATE: 01/13/93 WORK UNIT # 3362

DETAIL SUMMARY SHEET

TITLE: Immunologic Evaluation of Acute and Persistent Ectopic Gestation: A Collaborative Project with Portsmouth Naval Hospital

KEYWORDS: immunologic, ectopic, gestation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the immunologic systems of women with normal, acute ectopic, and persistent ectopic gestations.

TECHNICAL APPROACH
Subjects will be enrolled at Portsmouth Naval Hospital. Blood samples will be collected there and distributed to the laboratories conducting tests. WRAMC will perform lymphocyte subset analysis using monoclonal antibodies and two-color flow cytometry. HLA typing will be performed by a cytotoxicity assay with microscopic examination.

PRIOR AND CURRENT PROGRESS
Lymphocyte subset analysis has been performed on 13 samples since the last report for a total of 28. HLA typing has been performed on four samples since the last reporting date, for a total of 11.

CONCLUSIONS
The study is in the data collection stage, and no conclusions have been drawn yet. Samples are being analyzed by lymphoctye subset analysis and HLA typing, and these methods are working well.

REPORT DATE: 04/15/93 WORK UNIT # 3363

DETAIL SUMMARY SHEET

TITLE: Stability of Cat and House Dust Mite Allergens in Allergy Immunotherapy Preparations

KEYWORDS: allergens, stability, ELISA

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 1,090 Previous FYs: $ 64 Total: $ 1,154

STUDY OBJECTIVE
To measure at intervals over a year, fel d1, F1, and P1, in mixtures of cat or house dust mites with WRAMC grass, tree, weed, and mold groups of antigens.

TECHNICAL APPROACH
House dust mite or cat allergen extracts are combined with various mixtures of commonly used allergen immunotherapy preparations to test the effect these preparations have on levels of specific allergen proteins, fel d1, F1, and P1. The specific allergen proteins are measured with monoclonal antibody based enzyme-linked immunosorbent assays (ELISA).

PRIOR AND CURRENT PROGRESS
Preliminary studies are finished, and the study is underway. Two site capture assays have been established and work well. There are no human subjects involved in this study.

CONCLUSIONS
The study is ongoing; no conclusions on degradation of specific allergen by proteolytic or physical processes can be drawn yet.

REPORT DATE: 05/18/93 WORK UNIT # 3364

DETAIL SUMMARY SHEET

TITLE: Effect of N-(Fluorenyl-9-methoxycarbonyl)-L-Leucine (FMOC-LEU) on Neutrophil Activation

KEYWORDS: flow cytometry, neutrophil, FMOC-Leu

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: May 1991

FUNDING: Current FY: $ 1,386 Previous FYs: $ 3,509 Total: $ 4,895

STUDY OBJECTIVE
To measure the effect of N-(Fluorenyl-9-methoxycarbonyl)-L-leucine (FMOC-Leu) on CD11b expression in neutrophils activated with chemotactic agents by flow cytometry.

TECHNICAL APPROACH
The assay will use whole blood and isolated granulocytes from normal subjects. Neutrophils will be activated with chemotactic agents, with and without FMOC-Leu. Measurements will be performed with a flow cytometer, forward light scatter, side scatter, and fluorescent light. Changes in chemotactic-induced CD11b expression caused by FMOC-Leu will be determined.

PRIOR AND CURRENT PROGRESS
A total of 14 subjects have been enrolled (7 this last reporting period). There have been no serious or unexpected adverse reactions, and no subjects have withdrawn from the study. Whole blood and isolated granulocyte assays of chemotactic agent-induced CD11b expression have been established. FMOC-Leu appears to inhibit CD11b expression induced by FMLP but does not inhibit the size change induced by this stimulator. Some variability was seen between assays. Isolated granulocytes were activated by the isolation procedure, while it appeared that plasma proteins might interfere with the whole blood assay. An alternative procedure using dextran sedimentation alone, in which the granulocytes are kept at 4 degrees C, was employed. The problems of premature neutrophil activation and plasma proteins were avoided.

CONCLUSIONS
Whole blood and isolated granuloctye assays of chemotactic agent-induced CD11b expression have been established. FMOC-Leu does inhibit expression on granulocytes of the adhesion protein CD11b. The compound may exert its anti-inflammatory effect in part by interfering with cellular adhesion.

REPORT DATE: 09/09/93 WORK UNIT # 3365

DETAIL SUMMARY SHEET

TITLE: Leucocyte Subset Analysis in Patients Treated with Intravenous Immunoglobulin (IVIG)

KEYWORDS: IVIG, phenotypic changes, immunological changes

PRINCIPAL INVESTIGATOR: Davis, William CPT MC
ASSOCIATES: Huh, Michael LCDR MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 708 Previous FYs: $ 11,276 Total: $ 11,984

STUDY OBJECTIVE
To further define the mechanism of high dose intravenous immunoglobulin (IVIG) in inflammatory and immunologic disorders.

TECHNICAL APPROACH
Sequentially measure lymphocyte phenotypes in patients treated with high dose IVIG, observing changes, and correlating these phenotypic changes with clinical response.

PRIOR AND CURRENT PROGRESS
The study has been completed, and no new subjects are being enrolled. Nine patients have been studied altogether; four this past year. There have been no serious or unexpected adverse reactions, and no patients have withdrawn from the study. The study is being kept open to prepare a publication.

CONCLUSIONS
The data is being prepared for final publication. The major finding has been that in some patients single dose IVIG is safe and potentially more effective than divided doses. A reversible inversion of the CD4/CD8 ratio that correlates with clinical response has been documented.

REPORT DATE: 08/16/93 WORK UNIT # 3366

DETAIL SUMMARY SHEET

TITLE: Bird Antigen Detection in the Home and IgG and IgG Subclass Titers in Healthy Bird Owners Versus Those With Hypersensitivity Pneumonitis

KEYWORDS: hypersensitivity, bird, immunoglobulin

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 478 Previous FYs: $ 4,027 Total: $ 4,505

STUDY OBJECTIVE
To measure bird antigen levels in the homes of pet bird owners, and to determine the persistence of bird antigen after the bird(s) is (are) removed from the home.

TECHNICAL APPROACH
Enzyme linked immunosorbent inhibition assays are used to measure bird antigen levels in samples of dust collected from several rooms in the home, including the room where the bird was kept.

PRIOR AND CURRENT PROGRESS
Methods have been developed to measure bird antigen in immunoassay techniques. Eleven subjects have been enrolled; one during this reporting period. Subjects continue to be enrolled as they are identified. However, since this disease is reasonably uncommon and strict enrollment criteria are being used, it is taking time to enroll the required number of subjects. No subjects have withdrawn, and there have been no serious or unexpected adverse reactions.

CONCLUSIONS
Methods have been developed to quantitate bird antigen samples collected in homes. Bird antigen persists for up to 18 months after removal of the bird(s). This may partly explain the persistence of symptoms in patients with bird fancier's hypersensitivity pneumonitis despite aggressive medical therapy.

REPORT DATE: 06/09/93 WORK UNIT # 3367

DETAIL SUMMARY SHEET

TITLE: Naive Versus Memory T Lymphocytes in Patients Undergoing Aeroallergen Immunotherapy

KEYWORDS: lymphoctyes, aeroallergen, immunotherapy

PRINCIPAL INVESTIGATOR: Carregal, Valerie CPT MC
ASSOCIATES: Davis, William MAJ MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $11,501 Previous FYs: $ 2,573 Total: $ 14,074

STUDY OBJECTIVE
To measure memory and naive T cell subsets in patients undergoing aeroallergen immunotherapy and compare with age and sex matched allergic controls.

TECHNICAL APPROACH
These subjects of T lumphocytes, as well as basic cell surface markers, will be measured by flow cytometry before and at intervals during immunotherapy.

PRIOR AND CURRENT PROGRESS
As of June 1993, a total of 14 patients have been enrolled; 8 have completed the protocol. Six patients are projected to complete the study within the next 9 months, and enrollment is now closed. There have been no serious or unexpected adverse reactions from the blood draws. Patients on aeroallergen immunotherapy have benefited from this therapy for allergies. No one has withdrawn from the protocol.

CONCLUSIONS
To date, with completion of evaluation of eight subjects, there has been no evidence of change in memory and naive lymphocyte subsets in aeroallergen immunotherapy subjects as compared with allergic controls.

REPORT DATE: 09/17/93 WORK UNIT # 3368

DETAIL SUMMARY SHEET

TITLE: ELISA Measurement of the Humoral Immune Response to a Primary Rabies Vaccine Series

KEYWORDS: vaccination, immune response, immunodeficiencies

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 3,167 Previous FYs: $ 0 Total: $ 3,167

STUDY OBJECTIVE

To measure antibody production in patients immunized with the rabies vaccine. A detailed measurement will be useful both as an indicator of rabies protection, and as an aid in the evaluation of a patient's ability to respond to new antigens. This will be most useful when patients with possible immunodeficiences are considered.

TECHNICAL APPROACH

A group of about 35 subjects will be recruited to this study, consisting of patients undergoing a primary pre-exposure rabies vaccine series. Blood samples will be obtained on three occasions: prior to immunization, 40 days later (10 days after the completed series), and 60 days later (30 days after the completed series). A series of ELISA assays will be run to determine the specific antibody responses (IgG, IgA, IgM, IgG1, IgG2, IgG3, or IgG4) to the two major antigenic epitopes of the rabies vaccine.

PRIOR AND CURRENT PROGRESS

A total of 29 subjects were enrolled in this study. Two blood samples have been obtained from 18 subjects and three samples from 16. Refinements in an IgG ELISA were made, utilizing non-virus infected extract as a negative control, but further standardization of the assay is necessary and will require another batch of CDC prepared antigen. IgG to the N protein of the rabies virus was measured in all patient samples in the complete series. Assay parameters for the IgG subclass assay, using rabies immune globulin as a test sample, were determined. Preliminary IgA and IgM assays were run. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Study is ongoing. Although the IgG response to the rabies nucleoprotein (N protein) after three doses is moderate, there is minimal loss of titer 30 days following completion of the vaccination schedule.

REPORT DATE: 10/15/92 WORK UNIT # 4804

DETAIL SUMMARY SHEET

TITLE: Antigen Typing Reticulocytes in Mixed Red Blood Cell Populations by Flow Cytometry

KEYWORDS: flow cytometry, reticulocyte, red cell antigens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To develop a procedure to determine the red cell antigen phenotype of a recently transfused patient using a sample containing both patient and donor blood.

TECHNICAL APPROACH

The approach being developed is a dual staining technique followed by analysis with a flow cytometer. The presence or absence of a particular red cell antigen is detected using the fluorescent stain phycoerythrin (PE) in an indirect antiglobulin procedure. Reticulocytes are stained with a second fluorescent stain, thiazole orange (TO). If you assume that the reticulocytes are from the patient, then the phenotype of the reticulocyte is the patient's phenotype.

PRIOR AND CURRENT PROGRESS

Antigen phenotyping and reticulocyte identification have been performed on 319 mixed red cell samples using a flow cytometric method developed in this project. Antigen positive and negative cells in both mature red cell and reticulocyte populations could be readily differentiated. Excellent results were obtained with antisera to Rh0, K, Fya, Fyb, Jka, and c(hr'). The S antigen proved to be a difficult problem, probably because it is only sparsely expressed on red cells. Samples from 19 patients were tested, and in the vast majority of cases the results agreed with the manual method which was the gold standard. The few disagreements occurred when there were too few reticulocytes or if the S antigen was involved. No false positives were recorded. After a few more details are finished this protocol will be concluded, most likely within the next 6 months.

CONCLUSIONS

A simple, two-color flow cytometric method to phenotype mature red cells and reticulocytes was developed. This method correctly identifies the red cell antigen phenotypes in transfused patients. The method was applied to samples from patients who had received one unit of blood or who were massively transfused or chronically transfused.

REPORT DATE: 09/14/93 WORK UNIT # 4811

DETAIL SUMMARY SHEET

TITLE: Documentation of Irradiated Lymphocyte Inactivation Using the CD69 Surface Marker and Flow Cytometry

KEYWORDS: flow cytometry, irradiator, CD69

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 1,894 Previous FYs: $ 6,611 Total: $ 8,505

STUDY OBJECTIVE

To measure mitogen inducible lymphoctye activation in irradiated whole blood using lymphocyte cell surface activation markers and flow cytometry.

TECHNICAL APPROACH

The effects of gamma irradiation of whole blood on mitogen stimulated lymphocyte activation in cultured whole blood or ficoll-hypaque gradient purified lymphocytes will be measured. Immunostaining with fluorescently labelled mouse monoclonal antibodies to lymphocyte cell surface activation markers with two color cytometric analysis, as well as 3 H-thymidine incorporation, will be used to measure lymphocyte activation.

PRIOR AND CURRENT PROGRESS

Whole blood culture proved to be a poor method. Mitogen activation of lymphocytes was not vigorous enough. Freshly isolated lymphoctyes worked best in both thymidine incorporation and flow cytometric methods. CD69 expression worked well and gave results similar to the thymidine incorporation method which served as the gold standard. Interestingly, measurement of cell death worked as well as the other methods. Nineteen subjects have been enrolled in the project; none this past year. No subject withdrew, and there were no serious or unexpected adverse reactions.

CONCLUSIONS

Flow cytometric methods were developed to measure lymphocyte activation in post irradiation whole blood samples using measures of cell death and lymphocyte cell surface activation markers. These methods have the promise of being useful in the quality control of irradiators used to inactivate lymphocytes in units of blood to prevent post transfusion graft versus host disease.

REPORT DATE: 09/14/93 WORK UNIT # 4812

DETAIL SUMMARY SHEET

TITLE: Quantitation of Red Cell Phenotypes in a Dual Population by Flow Cytometry

KEYWORDS: flow cytometry, red cells, phenotype

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 1,268 Previous FYs: $ 2,623 Total: $ 3,891

STUDY OBJECTIVE
To develop methods to differentiate and quantitate red cells in a mixed cell population.

TECHNICAL APPROACH
Immunostaining with standard blood bank serum, Rh immunoglobulin, and fluorescently labeled anti-human IgG in conjunction with three parameter flow cytometry will be used to develop these methods. The parameters used will be forward light scatter (measures size), side light scatter (measures internal cellular complexity), and green fluorescent light output (measures antibody binding).

PRIOR AND CURRENT PROGRESS
Methods were developed to phenotype and quantitate red cells in a mixed cell population. The problem of multicellular aggregates which limit other methods was investigated, and the points where aggregates form were identified. The drawbacks of other methods were overcome using F(ab) fragments of anti-human IgG. In short, quantitative red cell phenotyping methods were developed using standard blood bank typing and commercially available fluorescein labeled anti-human IgG. Human subjects are not involved in this project.

CONCLUSIONS
Flow cytometric quantitative red cell phenotyping methods were developed using standard blood bank typing and commercially available fluorescein labeled anti-human IgG. This method used steadily available commercial reagents and should provide a useful tool for blood bank serologists when they are faced with mixed red cell populations.

REPORT DATE: 11/16/92 WORK UNIT # 6276

DETAIL SUMMARY SHEET

TITLE: In Vivo Persistence of Reticulocyte and Antigen Phenotype in Post-Transfusion Patients Analyzed by Flow Cytometry

KEYWORDS: reticulocyte, blood transfusion, flow cytometry

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Cooper, Louis CAPT MC; Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 1,080 Previous FYs: $ 1,294 Total: $ 2,374

STUDY OBJECTIVE

To determine the in vivo time course of homologous reticulocyte survival of recently transfused patients.

TECHNICAL APPROACH

Peripheral blood specimens will be collected from patients immediately before transfusion, immediately after completion of transfusion, and 3, 6, 12, 24, 48, and 72 hours later. Donor and recipient blood samples will be phenotyped for 12 different red cell antigens. The reticulocyte members for both antigen positive and antigen negative reticulocytes will be determined using a two-color flow cytometer procedure developed in our laboratory. The absolute reticulocyte numbers and relative proportions will be analyzed.

PRIOR AND CURRENT PROGRESS

Specimens have been collected and analyzed from 16 hematologically abnormal patients, with 3 subjects enrolled this past year. All but one of the subjects were pediatric patients. In 50% of the patients, donor reticulocytes persisted for 48 hours, and in two cases they were detectable at 72 hours. In two patients with relatively low pretransfusion reticulocyte counts, donor reticulocytes predominated soon after transfusion. No other patterns were discernable, probably related to the diversity of the patient sample. There have been no adverse reactions, and no subject has withdrawn from the study.

CONCLUSIONS

Donor reticulocytes may represent a significant portion of total reticulocytes in post transfusion samples collected within 72 hours and, consequently, create potential for misinterpretation of post-transfusion reticulocyte testing. Final conclusions await the completion of the study.

REPORT DATE: 09/14/93 WORK UNIT # 9272

DETAIL SUMMARY SHEET

TITLE: Relationship of Major Histocompatibility Complex Class II Genes to Inhibitor Antibody Formation in Hemophilia A

KEYWORDS: inhibitor, hemophilia A, histocompatibility

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Fisher, Lyman MD PhD; Kapur, Janet BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 35,616 Total: $ 35,616

STUDY OBJECTIVE
To identify a marker or trait which will prospectively identify the hemophilia A subpopulation at risk for developing anti-factor VIII inhibitor antibodies, and to substantiate a statistical association between the inhibitor phenotype and the major histocompatibility complex (MHC) using HLA testing.

TECHNICAL APPROACH
The HLA phenotypes of both inhibitor and non-inhibitor hemophilia patients will be determined by microlymphocytotoxicity. Restriction fragment length polymorphism (RFLP) analysis will be performed on peripheral blood DNA digested with a battery of restriction enzymes, Southern blotted, and probed with class II MHC alpha and beta gene probes.

PRIOR AND CURRENT PROGRESS
This study is completed. DNA was extracted on 16 samples, for a total of 133 samples. Complete HLA typing by microlymphocytotoxicity methods was performed on 50 samples. Five new subjects were enrolled in the project by Dr. Fisher's group at the Medical College of Virginia in Richmond, VA, where all subjects are enrolled. A total of 50 subjects have been enrolled to date.

CONCLUSIONS
The study is completed. No correlation between anti-factor VIII inhibitor phenotype and HLA type was seen.

REPORT DATE: 06/15/93 WORK UNIT # 9286

DETAIL SUMMARY SHEET

TITLE: Major Histocompatibility Complex DNA Typing of Hemophilia A Patients

KEYWORDS: Hemophilia A, HLA-DQ, inhibitor

PRINCIPAL INVESTIGATOR: Salata, Kalman, Ph.D., DAC
ASSOCIATES: Kapur, Janet BSc(MT); Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 6,534 Previous FYs: $ 1,738 Total: $ 8,272

STUDY OBJECTIVE
To establish a genetic marker that will identify the hemophilia A patients at risk for developing anti-factor VIII inhibitor antibodies (inhibitors) using recently developed typing techniques.

TECHNICAL APPROACH
Polymerase chain reaction (PCR), southern blotting, synthetic oligonucleotides, and dot blotting are to be used to examine HLA-DQ polymorphism.

PRIOR AND CURRENT PROGRESS
Genomic DNA has been amplified and tested on gels. Amplified DNA has been put on dot blots and tested with oligonucleotide probes, a consensus sequence, and four specific probes. There are no human subjects in this protocol.

CONCLUSIONS
PCR methods for HLA typing are being established. Studies are still ongoing; no conclusions can be drawn at this time.

REPORT DATE: 05/17/93 WORK UNIT # 1673

DETAIL SUMMARY SHEET

TITLE: Molecular Basis of the Maturation of Bone Marrow Granulocytes: Isolation, Purification and Characterization of Granulocyte Maturation Regulators from Normal Human Serum

KEYWORDS: granulocytes, maturation, regulator

PRINCIPAL INVESTIGATOR: Bednarek, Jana PhD
ASSOCIATES: Ward, Frank LTC MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 5,469 Total: $ 5,469

STUDY OBJECTIVE

To isolate, purify, and characterize the granulocyte maturation-inducing activity detected in normal human serum in the previous pilot study (Work Unit #1649-87).

TECHNICAL APPROACH

Chromatographic and electrophoretic procedures will be used to isolate, purify, and characterize the activity which is suspected to be a protein or peptide. At every step of purification, assays for biological activity will be performed in cultures of normal neutrophilic precursors from bone marrow. Attempts will also be made to use leukemic cell lines. When sufficiently purified, the molecule will be characterized by determination of molecular weight and amino acid composition. If it contains carbohydrates, the molecule's composition as well as its importance for biological activity/activities will be determined.

PRIOR AND CURRENT PROGRESS

Fifteen subjects have donated bone marrow alt gether; none this past year. The purification of maturation activity was carried out to a third step. Step 1 used DEAE fractogel displacement chromatography at 4 C in phosphate buffer pH 7.0. Step 2 used DEAE fractogel at pH 8.6 with Tween-20 to minimize losses in activity (approximately 1% of protein remained; most albumin and transferrin were removed). Activity was stable approximately 2 months at 4 C, but lost on freezing. Step 3 involved separation by HPLC based on hydrophobicity, and step 4 used electrophoretic separation and transblot of the protein. Activity is easily lost; to maintain it will require further experiments. Effects on CD-34 cells and leukemic cell lines were very promising and attracted attention of Miles Labs. Experiments were stopped because the PI was reassigned and the associates and collaborators retired or were given other assignments.

CONCLUSIONS

Purification proceeded of the activity involved in initiation or substantial regulation of granulocyte maturation, so there is a partially purified material showing three major bands and several minor bands (visible on overload of electrophoresis). Biological assays with step 1 and 2 CD-34 cells show reactions consistent with induction or recruitment by maturation factor. Leukemic cell lines Red-3 and HL-60 can be stopped from dividing.

REPORT DATE: 10/04/93 WORK UNIT # 9271

DETAIL SUMMARY SHEET

TITLE: The Ventilatory Response to Carbon Dioxide in Compensated Hepatic Cirrhosis

KEYWORDS: GABA, respiratory control, cirrhosis

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation STATUS: Completed
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 13,141 Total: $ 13,141

STUDY OBJECTIVE
To examine the potential role for gamma-aminobutyric acid (GABA) in the regulation of respiration.

TECHNICAL APPROACH
Noninvasive assessments of respiratory function and the pattern of breathing during hypercapnic rebreathing will be performed in subjects with cirrhosis of the liver and in normal controls.

PRIOR AND CURRENT PROGRESS
Eleven subjects have been studied to date; none this past year. An addendum was submitted in FY89 to correlate the decrease in ventilation with increases in serum GABA, but too few subjects have been enrolled since then to make any meaningful conclusions. The early work demonstrated a reduced ventilatory drive in patients with compensated cirrhotic liver disease. Recently, increased interest has prompted the researchers to consider writing a new protocol to answer additional questions related to breathing in patients with chronic hepatic cirrhosis.

CONCLUSIONS
Respiratory disease and ventilation are reduced in patients with compensated cirrhotic liver disease.

REPORT DATE: 11/02/92 WORK UNIT # 9275

DETAIL SUMMARY SHEET

TITLE: Quantitation and Characterization of EGF Levels in Rat Milk

KEYWORDS: EGF, milk, rat

PRINCIPAL INVESTIGATOR: Schaudies, Paul MAJ MS

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 16,791 Total: $ 16,791

STUDY OBJECTIVE
To examine the levels of epidermal growth factor (EGF) present in rat milk. To identify immunoreactive species of EGF and determine relationship to standard r-EGF. To characterize forms regarding their biological activities in vitro. To determine the functional roles of the multiple forms of biologically active EGF present in normal rat milk.

TECHNICAL APPROACH
Radioimmunoassay of diluted whole rat milk. Generation of an affinity resin against rat EGF. Affinity extraction of immunoreactive material in milk. Native polyacrylamide gel electrophoresis of affinity purified materials. Extraction of activity from gels. Assay of activity for receptor binding and induction of DNA synthesis.

PRIOR AND CURRENT PROGRESS
This study has determined that levels of EGF in the gastrointestinal tract of suckling rats is provided from mother's milk rather than local synthesis. Results have demonstrated hormonal control of EGF levels within the pancreas and kidney of the suckling rat. T3 causes an increase in renal EGF levels, whereas cortisone causes an increase in EGF in the pancreas of suckling rats.

CONCLUSIONS
As above.

REPORT DATE: 04/14/93 WORK UNIT # 9284

DETAIL SUMMARY SHEET

TITLE: Comparison of the Hela Cell Monolayer Vs. the Toxi-titer System for Their Respective Ability to Detect Clostridium Difficile Toxin B in Stool Filtrate

KEYWORDS: C. difficile, toxin B, assay

PRINCIPAL INVESTIGATOR: Dobek, Arthur PhD
ASSOCIATES: Rothman, Sara PhD; McEvoy, Peter MAJ MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 3,892 Previous FYs: $ 1,900 Total: $ 5,792

STUDY OBJECTIVE

To compare two diagnostic tests for reliability detecting Clostridium difficile toxin B in patient stool filtrates; a commercial human foreskin fibroblast cell assay (toxi-titer) and a cytotoxicity assay on HeLa cell monolayers cultured at WRAIR. The latter is a historical standard that can detect as little as 1 pg of toxin B. Data will be compared with toxin A positive data detected by a commercial microtiter assay kit using the same stools.

TECHNICAL APPROACH

Stools sent to the Clinical Microbiology Laboratory, WRAIR, for C. difficile toxin assay are utilized. These stools were originally tested by the clinical lab for toxin A by a commercial latex bead agglutination test; however, this test has been discontinued because it does not detect toxin A. To compensate for this missing information, the DCI laboratory now uses a commercial microtiter plate assay for toxin A to test all frozen stool aliquots in batches of 89 specimens. Those found positive, as well as a negative series, will be tested as a batch for toxin B by HeLa cell and toxi-titer assays.

PRIOR AND CURRENT PROGRESS

A total of 639 stool specimens from 525 patients (216 this past year) have been tested for toxin A, using the Toxititer ELISA microtiter plate system. Approximately 10% (66) of these specimens were positive for toxin A. Of the 12 patients with multiple specimens who were positive for toxin A, only 3 had all specimens which were positive. The remaining nine patients had only one positive specimen each. A total of 57 patients with multiple specimens were negative for toxin A. Fifty patients with only one specimen each were positive for toxin A. When all patients with at least one positive specimen are combined, there are 62 patients, or approximately 12% of the 525 patients tested in the study. A total of 85 positive specimens are necessary for statistical analysis. Thus, at a 10% positive rate, approximately 190 more specimens are needed.

CONCLUSIONS

Data indicates that 75% of the positive specimens were derived from 50 patients with only one specimen each in the study, and that of the 69 patients with multiple specimens, only 17% of them were positive at least once. The multiple specimen positive patients have almost double (17%) the positive rate compared to the single specimen positive patient rate (9%).

REPORT DATE: 01/13/93 WORK UNIT # 9285

DETAIL SUMMARY SHEET

TITLE: Honey: Antibacterial Activity Against Multiple Antibiotic Resistant Clinical Isolates In Vitro

KEYWORDS: antibacterial agent, clinical isolate, honey

PRINCIPAL INVESTIGATOR: Dobek, Arthur Ph.D.
ASSOCIATES: Klayman, Daniel PhD

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 335 Previous FYs: $ 1,394 Total: $ 1,729

STUDY OBJECTIVE

To determine: (1) whether commercial honey and any of its specific components can inhibit clinical isolates in vitro, especially those resistant to one or several antibiotics; (2) the identity of the antibacterial agents in honey; and (3) whether honey from different plant sources have varying antibacterial activity based upon the concentration or presence of the inhibitory agents.

TECHNICAL APPROACH

Thirty-nine clinical isolates each of Escherichia coli, Proteus mirabilis, Enterobacter spp, Pseudomonas aeruginos, Klebsiella spp, and multiple antibiotic resistant Staphylococcus aureus will be tested for inhibition by commercial pure honey samples from four different plants (clover, alfalfa, orange blossom, and safflower) using agar well diffusion. In addition, a limited amount of sugar-free clover honey extract will be compared with pure clover honey for inhibition against five isolates of S. aureus and of E. coli. All tests will be done in duplicate with a range of honey concentrations from 80% to 0.625%. Cultures will be considered sensitive if the zones of inhibition are at least 10 mm in diameter.

PRIOR AND CURRENT PROGRESS

Regardless of the plant source of the honeys tested, all 39 isolates of each bacterial genus were either sensitive or resistant. The isolates sensitive to the following percent concentrations of honey were: E. coli and Enterobacter spp, 20-10% concentration; P. mirabilis, 5-2.5% concentration; and S. aureus, 2.5-1.25% concentration. P. aeruginosa and Klebsiella spp were resistant. The sugar-free clover honey extract was just as inhibitory as the pure honey, with the five S. aureus isolates sensitive to 1.25% concentration and the five E. coli isolates sensitive to 5% concentration of both agents. Thus, sugar may not be the only inhibitory agent in the honey.

CONCLUSIONS

The antibacterial agents in honey may be similar, regardless of the plant source. The agents are not exclusively the sugars, at least for clover honey. The sensitivity of all 39 isolates of a particular genus suggests the absence of pre-existing natural resistance to the antibacterial agent. The mechanisms involved in antibiotic resistance and inhibitor resistance are not the same in the agent-sensitive genera.

REPORT DATE: 01/07/93 WORK UNIT # 9411

DETAIL SUMMARY SHEET

TITLE: Evaluation of Collagen Plugs to Prevent Localized Osteitis in the Sockets of Mandibular Third Molars Susceptible to Acute Pericornitis

KEYWORDS: collagen, plugs, osteitis

PRINCIPAL INVESTIGATOR: Patterson, Adrian COL DC
ASSOCIATES: Baumgartner, John DDS; Glenn, Roger MAJ DC

SERVICE: Dental Clinic STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if collagen plugs are useful in preventing postoperative alveolar osteitis in third molar tooth sockets susceptible to pericoronitis. To determine if collagen plugs are useful in preventing postoperative alveolar osteitis in third molar tooth sockets which were susceptible to pericoronitis.

TECHNICAL APPROACH
This is a multi-center study. Each practitioner will extract approximately 100 third molars susceptible to pericoronitis. Patients will be randomly selected to either receive or not receive a collagen plug in the third molar socket after extraction. The patient will be evaluated 7 days post surgery to determine if a dry socket or any other sequelae is present.

PRIOR AND CURRENT PROGRESS
Since the study began, 162 patients have been enrolled; none have been enrolled during this past reporting year. Patient treatment has been stopped at this time due to PCS moves by MAJ Glenn and MAJ Peck. There have been no adverse reactions noted in any patient.

CONCLUSIONS
Data has been collected and is being analyzed for statistical significance. A determination will then be made to report existing data, continue, or close the study.

REPORT DATE: 04/01/93 WORK UNIT # 9412

DETAIL SUMMARY SHEET

TITLE: Comparison of Presurgical and Postsurgical Condylar Measurements as a Function of Orthognathic Surgical Fixation Technique

KEYWORDS: condylar measurements, mandibular movement

PRINCIPAL INVESTIGATOR: Brousseau, Steven LTC DC

SERVICE: Dental Clinic STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To measure changes in the temporomandibular joint (TMJ) that result from mandibular and/or mandibular-maxillary surgery, using presurgical and postsurgical (3-month, 6-month, 9-month) pantographic tracings to correlate clinical symptoms/signs with changes in condylar path tracings. The goal will be to try to use this information to predict problems with specific surgical movements and the use of rigid vs non-rigid fixation.

TECHNICAL APPROACH

Tracing of the condylar pathway during mandibular movement is a noninvasive diagnostic technique that allows quantitative and qualitative analysis of TMJ function. With a condylar path recording device, disk-condyle incoordination can be seen as a deviation or obstruction in the tracing pathway. The condylar path tracing can be translated into a PRI score, which can be used to compare and to correlate with clinical TMJ findings.

PRIOR AND CURRENT PROGRESS

There are 18 patients enrolled in this study; 3 in the control group; 8 in the rigid fixation group (6 complete and 2 with 9-month follow-up pending); and 5 in the non-rigid fixation group (2 complete and 3 with 9-month follow-up pending).

CONCLUSIONS

No analysis at this point.

REPORT DATE: 05/05/93 WORK UNIT # 9088

DETAIL SUMMARY SHEET

TITLE: Prevention of Low Back Pain in Military Basic Trainees

KEYWORDS: low back pain, prevention, smoking

PRINCIPAL INVESTIGATOR: O'Connor, Francis CPT MC
ASSOCIATES: Marlowe, Sarah CPT MC

SERVICE: Fort Dix, New Jersey STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence and risk factors of low back pain (LBP) in military basic trainees; and to evaluate the role of exercise in preventing low back pain.

TECHNICAL APPROACH
Entry and exit survey questionnaires will be administered to evaluate subjective LBP in basic trainees, as well as detailed demographic data. Specific exercises will be introduced into a control basic training company, and then reevaluated through entry and exit survey.

PRIOR AND CURRENT PROGRESS
Pilot study with demographic data has been completed. The pilot was written and accepted for abstract at USAFP in Oakland, California, as well as for publication by "Spine." The second aspect of this study has been completed. Currently, data is being analyzed. No more basic trainees are to be enrolled. A final paper is being written at this time.

CONCLUSIONS
Results from the pilot study document there is a significant incidence and prevalence of LBP in military basic trainees. History of chronic low back problems was associated with difficulty in completing basic training. Our preliminary data suggests that there was no difference with the low back exercise intervention.

REPORT DATE: 01/27/93 WORK UNIT # 1952

DETAIL SUMMARY SHEET

TITLE: The Clinical Presentation of HIV Infected Patients at Walter Reed Army Medical Center

KEYWORDS: HIV, epidemiology, disease progression

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Chung, Raymond COL MC; Hicks, Charles LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate clinical and laboratory data on the first 402 adults seen in clinic at WRAMC who are infected with HIV-1 by retrospectively reviewing their records.

TECHNICAL APPROACH
Chart review of medical records and laboratory studies on HIV infected patients.

PRIOR AND CURRENT PROGRESS
CD4 counts decrease with time in an exponential fashion. Life is prolonged with Zidovudine (AZT) and/or pneumomystis prophylaxis. With these therapies, CD4 cell counts do not correlate with prognosis. Other prognostic markers are needed in these patients. To date, 172 charts have been reviewed; none this past year.

CONCLUSIONS
CD4 counts decrease with time in an exponential fashion. Life is prolonged with Zidovudine (AZT) and/or pneumomystis prophylaxis. With these therapies, CD4 cell counts do not correlate with prognosis. Other prognostic markers are needed in these patients.

REPORT DATE: 05/20/93 WORK UNIT # 1953

DETAIL SUMMARY SHEET

TITLE: The Generation of Human Monoclonal Antibodies to the HIV

KEYWORDS: monoclonal, HIV, human

PRINCIPAL INVESTIGATOR: Drabick, Joseph MAJ MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
The purpose of this study is to generate human monoclonal antibodies to commercially available recombinant HIV antigen from the lymphocytes of patients infected with HIV.

TECHNICAL APPROACH
B. lymphocytes from peripheral blood or available lymphoid tissues are separated, then transformed with EBV. The transformed lymphocytes are screened for antibodies to HIV, recombinant HIV antigens, and recombinant soluble CD4. Positive wells are fused to heteromyeloma SHM-D33-0 and screened for specific antibody production. We are currently experimenting with MAB production from EBV transformed B cells and transfect other cell lines for better MAB.

PRIOR AND CURRENT PROGRESS
To date, 14 patients have been enrolled in this study (all during the past year). There have been no serious or unexpected adverse reactions. Immortalized human B cells which secrete antibodies to parts of HIV, as well as CD4, have been produced, but there has been no success in establishing stable, high producing hybridomas. Despite some new promising approaches, progress on this study has been hampered over the past 2 years because of the loss of technical support personnel.

CONCLUSIONS
The protocol will be terminated at this time, although other approaches to specific hybridoma manufacture not requiring HIV-infected humans via the protocol may continue (e.g., in vitro immunization, humanization of murine monoclonal antibodies).

REPORT DATE: 09/30/93 WORK UNIT # 3342

DETAIL SUMMARY SHEET

TITLE: Delayed Type Hypersensitivity Skin Testing: Correlation of Intradermal Injection Vs. Epicutaneous Antigen Placement and CD4 Number in Normals and HIV Seropositive Subjects

KEYWORDS: DTH, skin test, multitest

PRINCIPAL INVESTIGATOR: Birx, Deborah LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To correlate antigen reactivity by intradermal (ID) and epicutaneous injection to circ. CD4 number; compare subject reactivity to each of the antigens: tetanus, Candida, Trichophyton IC/multitest correlate anergy by multitest, and ID injection with evidence of HIV disease progression; and develop a standardized anergy panel to clinical staging of HIV infected patients.

TECHNICAL APPROACH
Simultaneous application of the multitest and ID injection of antigens in HIV infected patients.

PRIOR AND CURRENT PROGRESS
This protocol has had difficulties meeting the expected enrollment. There was reluctance from some patients to receive the multitest. As a result, only 100 patients were enrolled which has made analysis difficult. No significant adverse events have occurred; no volunteers have been enrolled during this reporting period. Due to the reorganization of the WRAIR, this protocol will no longer receive funding and is terminated.

CONCLUSIONS
There are no conclusions as data analysis in this isolated cohort will not achieve the planned analysis for the trial. However, fusing the data with the NNMC cohort to evaluate the two testing techniques is being explored.

REPORT DATE: 10/18/93 WORK UNIT # 4806

DETAIL SUMMARY SHEET

TITLE: Pathological Manifestations of HIV Infections at Autopsy

KEYWORDS: cause of death, histology, microbiology

PRINCIPAL INVESTIGATOR: Anderson, David LTC MC
ASSOCIATES: Clark, Gary COL MC; Turnicky, Ronald LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To: 1) perform complete research autopsies on deceased patients with HIV disease; 2) document disease processes causing morbidity and mortality in patients enrolled in WRAMC HIV research; 3) obtain fresh tissue for immuno-histochemical detection phenotyping of immune cells and detection of viral infections; and 4) obtain fresh tissue from major organ systems to store in a tissue registry (unfixed at -70 C and formalin-fixed, paraffin-embedded).

TECHNICAL APPROACH
Complete autopsies will be performed as soon after death as a valid research autopsy permit is available. Tissues from all major organ systems will be examined and processed for histochemistry (formalin-fixed, paraffin-embedded) or flash frozen for immune cell phenotyping. Routine histochemistry, special stains, and immune cell phenotyping will be performed, as well as microbiologic culture. Results will be assembled into a research autopsy protocol report which will be returned to the Infectious Disease Service, the deceased patient's chart, and the Jackson Foundation data base.

PRIOR AND CURRENT PROGRESS
Twenty-two autopsies at WRAMC (7 during the last year), and 10 at NNMC (4 during the past year) revealed as causes of death (8 cases had 2 causes of death): 8 PCP; 4 Staph. sepsis; 4 HIV wasting only; 4 cardiomyopathy; 3 actue pneumonia; 3 KS; 5 other sepsis; 2 ARDS; 2 PML; 2 CMV encephalitis; 1 pancreatitis; 1 sudden death; and 1 adenovirus pneumonia. A quantitative imaging technique was developed to allow in situ quantitation of immune cell phenotypes in solid human parenchymal tissues; very few lymphocytes are present in parenchymal tissues at death and tend to be terminally differentiated B-lymphocytes. Tissue registries for most autopsies have been used to validate PCR detection of HIV proviral DNA in tissues at SRA Laboratories as well as M. avium intracellulare and P. carnii DNA in tissues at AFIP; and conduct survey of culturable mycoplasma species. No mycoplasma species were detected.

CONCLUSIONS
HIV patients dying at WRAMC are almost uniformly late stage (WRS6) due to patient factors (drug reactions, noncompliance); pneumonia due to P. carinii continues to represent the leading cause of death. Depletion of most T cells can be expected in all parenchymal tissues at death. Frozen tissue registries are most useful as reference material for evaluating new gene amplification diagnostic methods.

REPORT DATE: 08/02/93 WORK UNIT # 6220

DETAIL SUMMARY SHEET

TITLE: Epidemiology of HIV In Pediatric and Perinatal Patients - A Natural History Study

KEYWORDS: immunodeficiency, pediatric, epidemiology

PRINCIPAL INVESTIGATOR: Robb, Merlin LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a Military Pediatric HIV Program for identification of military dependents (spouses and children) of HIV infected personnel. The study will identify basic epidemiologic information and follow these high risk or HIV-infected children over time to assess infection status and disease progression.

TECHNICAL APPROACH
The Military Pediatric HIV Program will identify children at high risk for HIV infection by matching USAHDS reports with the computer linked DEERS data files. All families with one or both spouses infected with HIV will be offered voluntary enrollment in this program. In addition, children with illness or other problems associated with HIV infection may also be voluntarily enrolled in this study. All children followed will be periodically reevaluated using state-of-the-art HIV diagnostic tests. It is anticipated that this program will encompass Army, Air Force, and Navy dependents.

PRIOR AND CURRENT PROGRESS
A total of 203 patients (83 from WRAMC) have been enrolled; 57 (8 from WRAMC) this past year. Two naval hospitals (San Diego and Bethesda) are also participating. Thirty-three of the 203 patients enrolled have HIV. Seven of the eight study deaths were HIV related; six occurred prior to 36 months of life yielding a mean survival of 6.8 years. Study data has contributed to an analysis of normal values for T cell phenotypes in children and to diagnostic techniques for perinatal HIV exposure. The DOD cohort has observed a 18.6% transmission rate, with HIV culture giving the most sensitive and specific diagnosis. PCR is slightly more sensitive but is more likely to give false positive results. Transmission within typical households was not observed. However, peripartum transmission between discordant couples was seen in two of seven, reflecting a potential increase in transmission risk in the peripartum period.

CONCLUSIONS
Interpretation of T cell values in HIV + children is confounded by the dramatic changes in normal values during the first several years of life. Reliance upon CD4% expressed as a percentile of the normal distribution for age may improve the predictive value of T cell phenotypes in children. The long-term prognosis of military beneficiaries in this study is superior to that reported in most publications.

REPORT DATE: 09/30/93 WORK UNIT # 6222

DETAIL SUMMARY SHEET

TITLE: Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses

KEYWORDS: AIDS, diagnosis, cultures

PRINCIPAL INVESTIGATOR: Robb, Merlin MAJ MC
ASSOCIATES: Burke, Donald COL MC; Ascher, David MAJ MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
a) To analyze laboratory assays for detection of HIV infection in children; and
b) To correlate the results with the clinical status of the child.

TECHNICAL APPROACH
This protocol will evaluate the usefulness of new diagnostic assays for HIV as they are developed using blood from HIV-infected or high risk children. Blood will be sent to the laboratory for standard ("state-of-the-art") HIV testing (generally those tests that are most developed). The surplus will be utilized for less well developed assays or stored for future analysis. Results from all tests will be compared to conventional assays used to diagnose adult HIV infection (ELISA, Western Blot) to determine their usefulness in children.

PRIOR AND CURRENT PROGRESS
A total of 50 patients have been enrolled from WRAMC, to include 3 during the past year. An additional 84 patients have been enrolled in other participating sites, to include 5 this past year. The use of whole blood cultures for diagnosis of HIV in children was explored and was found to be efficient with respect to phlebotomy requirements, but modestly less sensitive than standard co-culture techniques. This study contributed to an analysis of normal T cell values in HIV infected and uninfected at-risk children to provide a basis for early recognition of HIV induced disease. A careful comparative analysis of several virologic methods for detecting and quantifying HIV were characterized using samples from infected and uninfected patients. The DOD beneficiary cohort has a perinatal transmission rate of 19.6% to date.

CONCLUSIONS
Sensitivity and specificity of HIV culture, PCR, whole blood culture, plasma culture, and p24 antigen capture have been defined. Large amounts of virus detected with these assays may identify patients with more advanced disease or a poor prognosis. A combination of virologic techniques is required to obtain an early diagnosis of HIV in perinatally exposed children.

REPORT DATE: 04/29/93 WORK UNIT # 6264

DETAIL SUMMARY SHEET

TITLE: Perinatal HIV Infection: Epidemiology and Natural History

KEYWORDS: natural history, perinatal HIV, epidemiology

PRINCIPAL INVESTIGATOR: Pettett, Gary COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a central perinatal program for the identification, evaluation, and follow-up of HIV-infected pregnant women and their newborn infants, and to describe the clinicopathologic correlates most predictive of perinatal transmission of HIV.

TECHNICAL APPROACH
High risk pregnant women and maternal-infant pairs are prospectively entered into a longitudinal study to evaluate immunologic status and detect vertical transmission of HIV infection in early infancy. Quarterly clinical examination and serologic/immunologic assays are utilized to fully characterize the immune status of all patients. Statistical analysis of clinical and laboratory results will be directed toward the identification of perinatal factors which are reliable predictors of vertical transmission.

PRIOR AND CURRENT PROGRESS
Altogether, 21 maternal-infant pairs have been enrolled at three participating military medical centers: WRAMC, National Naval Medical Center, and San Diego Naval Medical Center; 15 maternal-infant pairs during this reporting period. A total of 63 protocol visits have been completed. Twenty HIV infected women were identified last year in the DOD through a passive system of identification. However, few of these women could be enrolled due to the lack of protocol availability at their military treatment facilities. The protocol is being introduced to several additional medical centers. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
The apparent transmission rate, based upon this experience and the clinical evaluation of non-protocol patients, is 16.5% in the military beneficiary population. Seven HIV negative women (spouses are HIV positive) have participated in this protocol, and two have seroconverted, suggesting that the peripartum period is a particularly high risk period for sexual transmission.

REPORT DATE: 04/07/93 WORK UNIT # 6284

DETAIL SUMMARY SHEET

TITLE: Perinatal HIV Tissue Bank

KEYWORDS: fetal HIV infection

PRINCIPAL INVESTIGATOR: Pettett, Philip COL MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To accumulate placental and fetal membranes from HIV(+) parturient women for the express purpose of diagnosing and quantifying fetal HIV tissue infection.

TECHNICAL APPROACH
Placental and fetal membranes from consenting HIV(+) pregnant women will be collected and stored in preservative media appropriate for microscopic and histochemical identification of HIV infection.

PRIOR AND CURRENT PROGRESS
This protocol has received no funds, and no patients have been enrolled.

CONCLUSIONS
Request termination of this protocol.

REPORT DATE: 05/13/93 WORK UNIT # 6325

DETAIL SUMMARY SHEET

TITLE: Language and Neurodevelopment in Children with Perinatal Exposure to HIV

KEYWORDS: language, neurodevelopment, perinatal

PRINCIPAL INVESTIGATOR: Walker, William, LTC, MC
ASSOCIATES: Conlon, Charles MD; McCardle, Peggy PhD, MPH

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 1,106 Previous FYs: $ 0 Total: $ 1,106

STUDY OBJECTIVE
To document early central nervous system expression of perinatal human immunodeficiency virus (HIV) and to explore the relations among neurodevelopmental functions and disease progression in HIV infected and perinatally exposed children.

TECHNICAL APPROACH
Children with perinatally acquired HIV infection will be followed prospectively for 4 years and assessed quarterly during the first 12 months and then semi-annually while asymptomatic. Children in the control group will be matched for age, sex, SES, and race/ethnicity. Data will be analyzed using a repeated measures design. The neuropsychological battery will include functioning in the areas of global cognitive ability, speech/language processes, attention/behavior, and motor functioning.

PRIOR AND CURRENT PROGRESS
No funding or support personnel have been available for this project. As a result, no children have been entered into the study, and no data has been collected.

CONCLUSIONS
With the PCS of the current Walter Reed Principal Investigator, this study is being recommended for termination.

REPORT DATE: 04/12/93 WORK UNIT # 7243

DETAIL SUMMARY SHEET

TITLE: Psychiatric Natural History Study: Factors Related to Human Immunodeficiency Virus Transmission and Morbidity

KEYWORDS: HIV risk behaviors, early HIV disease, military performance

PRINCIPAL INVESTIGATOR: Tomoshok, Lydia PhD
ASSOCIATES: Nannis, Ellen PhD; Brandt, Ursula PhD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine potential areas for effective interventions designed to reduce HIV transmission by HIV-infected military medical beneficiaries, and to reduce neuropsychiatric complications of HIV disease progression in infected military medical beneficiaries.

TECHNICAL APPROACH

Military medical beneficiaries from all three services [500 from Walter Reed Army Medical Center, 700 from Wilford Hall (WHMC), 300 from National Naval Medical Center (NNMC), and 400 from San Diego Naval Hospital] will be asked to complete anonymous risk behavior assessments. Smaller numbers of infected individuals will be recruited to participate in other non-anonymous protocol core areas; psychosocial (N=1,400), psychiatry (N=1,000), stress and coping (N=1,000), and neuropsychology (N=500). These non-anonymous but confidential portions of the protocol will be repeated at each patient's routine medical re-evaluation.

PRIOR AND CURRENT PROGRESS

Data collection from the Anonymous, Seropositive Behavior Survey was completed March 1993; data collection for the Neurobehavioral Addendum will be completed by June 1993. Data collection continue for the psychosocial questionnaires at the WRAMC, NNMC, and WHMC sites. To date, 268 HIV+ have been enrolled at WRAMC, 212 at NNMC, and 703 at WHMC, and 25 from Womack Community Hospital, Ft. Bragg. HIV controls have been enrolled and assessed; 87 at WRAMC and 38 at NNMC. Thirty-six are enrolled in the neurobehavioral addendum. Data analysis is ongoing, and intervention protocols based on these data are in final development.

CONCLUSIONS

Longitudinal research and collection of seronegative control data are proceeding on or ahead of schedule. Two intervention protocols based on data from RV26 have received conditional approval by the USAMRDC Retrovirus Clinical Research Committee. Upon receipt of full scientific approval, these protocols will be forwarded to the appropriate Human Use Committees.

REPORT DATE: 05/03/93 WORK UNIT # 8802

DETAIL SUMMARY SHEET

TITLE: VA Cooperative Study No. 298, Treatment of AIDS and AIDS Related Complex; Part I: Treatment of Patients with ARC (AZT Vs. Placebo)

KEYWORDS: zidovudine, HIV, ARC

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Apr 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 996 Total: $ 996

STUDY OBJECTIVE

To determine the effectiveness of AZT (zidovudine) on AIDS Related Complex (ARC) - Walter Reed Stages 2-4.

TECHNICAL APPROACH

This is a randomized double-blind placebo-controlled study. Subjects who meet the inclusion criteria, after screening, are randomized onto the study drug. Half of the subjects receive AZT 250 mg every 4 hours, while the other half receive a placebo. In January 1991, Part I was completed; all participants were informed of their original treatment assignment and given the opportunity to remain or be started on open-label zidovudine or placebo. In February 1991, an addendum was approved which allowed for extended follow-up for all participants who agreed to continue and sign a revised informed consent. The extension was granted for 3 years (i.e., April 1994).

PRIOR AND CURRENT PROGRESS

No new patients were enrolled this past year. There have been no serious or unexpected adverse reactions. In Part II, 213 patients from Part I (9 from WRAIR, 2 expired) were enrolled and continued to be followed until the final endpoint, death, is reached. Results showed that Caucasian patients who received early AZT were less likely to progress to AIDS (p=0.007); however, for Black/Hispanic patients, there was no significant difference (p=0.45). Median survival in patients who received early AZT was 11.8 months, compared to 16.6 months in patients who received AZT later. There was no significant difference between early and later AZT in terms of quality of life, as measured by the Sickness Impact Profile (SIP), and the Time Without Symptoms or Toxicity Profile (SIP), and the Time Without Symptoms or Toxicity Profile (TWIST).

CONCLUSIONS

There continues to be no observed overall survival benefit to starting AZT early. Data regarding AZT resistance and its role in clinical progression is forthcoming. The observed, apparent, lack of efficacy in minorities remains unexplained. However, recent preliminary pharmacokinetic data suggest that AZT may have a shorter half-life in Blacks.

REPORT DATE: 05/14/93 WORK UNIT # 8803

DETAIL SUMMARY SHEET

TITLE: Core Protocol for HIV Developmental Diagnostics (Adults)

KEYWORDS: HIV, AIDS, virus culture

PRINCIPAL INVESTIGATOR: Turnicky, Ronald LTC MC
ASSOCIATES: Oster, Charles COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop and evaluate new and/or improved laboratory methods for establishing the diagnosis of HIV infection and for determining the stage of illness.

TECHNICAL APPROACH
Methods to detect replicating HIV virus, HIV antigens, and HIV nucleic acids will be used, including, for example, virus culture, antigen capture immunoassay, and polymerase chain reaction (PCR) amplification of HIV DNA.

PRIOR AND CURRENT PROGRESS
In the past 12 months, 2,651 patient samples were received in RV2. All specimens were processed to provide sera, plasma, and cells for analysis which consisted of 3,182 co-cultures for the HIV virus. Polymerase chain reaction (PCR) was performed on 460 samples for HIV and 91 for HTLV. Radioimmunoprecipitation was performed on 1,046 HIV and 418 HTLV sera samples. An acid disassociative technique was developed for the performance of 1,932 p24 antigen assays by ELISA. Additionally, 280 assays for anti-p24 antibody were conducted. All samples are retained for future use in a repository.

CONCLUSIONS
HIV is routinely identified for diagnostic purposes in serologic, nucleic acid, and co-culture techniques. Earlier detection of antibody response is being developed. Methods to serologically discriminate between retroviruses and methods to discriminate natural HIV infection from vaccine-induced antibody response are being developed.

REPORT DATE: 05/27/93 WORK UNIT # 8804

DETAIL SUMMARY SHEET

TITLE: The Natural History of HIV Infection and Disease in United States Military Beneficiaries

KEYWORDS: HIV, natural history, AIDS

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To systematically document the natural disease progression of HIV infection.

TECHNICAL APPROACH
Information already being routinely collected on HIV patients is being organized into a data base in such a way that more scientifically valid information will be forthcoming. Safeguards to patient confidentiality are met. This data base forms the core around which other specific protocols can be built.

PRIOR AND CURRENT PROGRESS
In the last year, 121 volunteers were enrolled; for a total of 681 actively enrolled at the end of this reporting period. From May 1992 to May 1993, 61 volunteers were terminated from the study: death (49), voluntary withdrawal (3), transfer to another area (2), and lost to follow-up (7). Several analyses have been done using the natural history study, including studies on the natural history of HIV infection in women, progression of disease based on the slope of the CD4 cell decline, demographic factors associated with compliance in taking AZT, and effects of AZT on the progression of HIV disease by WR stage. There are ongoing analyses examining the effect of the new CDC criteria on the incidence of AIDS in our population and examining the variability of CD4 counts obtained less than 30 days apart.

CONCLUSIONS
This study continues to collect valuable data on the natural history of HIV in military populations in cooperation with the Air Force (Wilford Hall, Lackland Hall, San Antonio, TX), the Navy (National Naval Medical Center, Bethesda, MD), Walter Reed Army Medical Center), and Brooke Army Medical Center, Fort Sam Houston, TX).

REPORT DATE: 10/15/92 WORK UNIT # 8805

DETAIL SUMMARY SHEET

TITLE: Natural History of Oral Manifestations of HIV Infection in a United States Military Population

KEYWORDS: epidemiology, oral diseases, HIV

PRINCIPAL INVESTIGATOR: Konzelman, Joseph DDS
ASSOCIATES: Swango, Philip CAPT USPHS

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To document the prevalence and incidence of oral manifestations of HIV infection in relation to the degree of immunodeficiency. Emphasis is given to oral pathologies, periodontal disease, oral candidal infections, and the effect of HIV on salivary constituents.

TECHNICAL APPROACH

Volunteers receive a comprehensive oral examination at entry and every 6 months thereafter. This evaluation includes clinical examinations for dental caries, periodontal disease, and oral mucosal pathologies. Dental plaque and saliva samples are collected for microbial and biochemical assays, and a questionnaire on oral health-related behaviors and history is administered. Data are analyzed in relation to subjects' medical condition and immune status.

PRIOR AND CURRENT PROGRESS

A total of 285 subjects were enrolled during the past year, bringing the current total to 946 enrollees. Of these, 638 have received their initial baseline oral examination, and 267 have also received at least one 6-month follow-up exam. No adverse reactions have been reported, and no patients have withdrawn from the study. Benefits to subjects include early diagnosis of oral disease, dental prophylaxis, limited emergency care, and referral for appropriate treatment.

CONCLUSIONS

Prevalence of oral mucosal pathology was 32% at baseline and 44% after 6 months of follow-up. More than 30% of subjects initially free of mucosal pathology developed oral lesions within 6 months. Oral candidiasis was the condition that developed most frequently, with 70% of incident cases being of the erythematous form.

REPORT DATE: 12/17/92 WORK UNIT # 8806

DETAIL SUMMARY SHEET

TITLE: Active Immunization of HIV Infected Patients with Recombinant GP160 HIV Protein: Phase I Study of Immunotherapy, Immunogenicity and Toxicity

KEYWORDS: rgp160, vaccine therapy, HIV

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the long-term safety and immunogenicity of vaccine therapy in early stage HIV infected patients, to evaluate variable boosting schedules, and to evaluate in vitro assays with in vivo relevance for application to Phase II trials

TECHNICAL APPROACH
During the primary extended immunization series, original trial responders will be vaccinated every 4 months (160 ug) and nonresponders at Day 0, 7, 30, 60, 90, and 120 (160 ug), and then every 4 months (160 ug). In March 1992, an addendum was approved by the HUC/IRB to vaccinate volunteers every month. Alterations in cellular and humoral immune responses to HIV specific proteins and changes in vivo and in vitro cellular immune function continue to be assessed.

PRIOR AND CURRENT PROGRESS
Twenty-eight of the 30 original trial volunteers continue evaluation in this Phase I study; patient accrual was completed during the first 2 years. Nine of 10 nonresponders displayed novel humoral and cellular immune responses after the 6-shot series. Responders displayed continued induction of humoral and cellular responses. Data derived from the every 4 month immunization series indicate a predictable boost in immune responses, temporally associated with vaccination followed by a response trough. Based on this pharmacokinetic data, an immunization series of every 1 month was started to compare boosting series. No systemic toxicity has been noted; local toxicity is limited. Several volunteers have developed notable soft tissue swelling intermittently associated with vaccination. Seven volunteers have been given AZT by primary physician; three have developed mean CD4 counts below 200 cells/mm3.

CONCLUSIONS
The rgp160 vaccine continues to be safe and immunogenic in early HIV infected individuals. Through the reimmunization of nonresponders we have been able to show majority response rates, regardless of CD4 counts and general health, which were originally predicted to limit vaccine applicability. Additionally, the vaccine is shown to continue to elicit immune responses without tolerance.

REPORT DATE: 05/07/93 WORK UNIT # 8812

DETAIL SUMMARY SHEET

TITLE: The Investigation of the Cutaneous Manifestations of HIV Infection in Relation to the Onset, Severity and Progression of Disease, Dermatologic Natural History

KEYWORDS: HIV, dermatology, Walter Reed stage

PRINCIPAL INVESTIGATOR: Smith, Kathleen COL MC
ASSOCIATES: Skelton, Henry CDR MC USN

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study cutaneous manifestations, both histologically and clinically, in relation to disease onset and progression of disease.

TECHNICAL APPROACH
A complete dermatology examination, including a complete history, is performed. Lesional biopsies (4-6 mm punch) are performed, as needed, for diagnosis. Lesional biopsies may be split and half frozen for performing immunohistochemical markers of the inflammatory infiltrate. In addition, special stains are performed to rule out infections. The patients are followed every 6 months and may be seen for problems that develop between visits. In addition, seven cutaneous sites are cultured for fungus and bacteria in patients in all stages of disease; repeat cultures are performed if the stage changes.

PRIOR AND CURRENT PROGRESS
A total of 1,053 subjects have been enrolled in this study; 81 during the past year. There has been no incidence of serious or unexpected adverse reactions. The related protocol (W.U. #8811) for cutaneous microflora in HIV-1 disease has been completed. The manuscripts on clinical, histologic, and immunohistochemical findings in HIV-1 disease have been published. A number of other manuscripts with clinical-histopathologic correlation of cutaneous findings and patterns of immune dysregulation in HIV-1 disease have been published.

CONCLUSIONS
The clinical findings are now being evaluated to determine if any particular one may be predictive of disease progression. Many cutaneous conditions reflect patterns of immune dysregulation in HIV-1 disease.

REPORT DATE: 08/20/93 WORK UNIT # 8814

DETAIL SUMMARY SHEET

TITLE: Pharmacoepidemiologic Study to Develop a Database to Document Variations in the Outcome of Illness Which May be Due to Drug Effects and To Document Patterns of Drug use in HIV Infected Patients

KEYWORDS: pharmacoepidemiology, data base, drug use

PRINCIPAL INVESTIGATOR: Cortese, Linda RPh, MS
ASSOCIATES: Oster, Charles COL MC; Hiner, William COL MS

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a data base to study outcomes of illness due to drug effects (both beneficial and adverse), and to gather useful information on drug use patterns of HIV infected patients.

TECHNICAL APPROACH
To develop a data base in conjunction with the Henry M. Jackson Foundation (HMJF) HIV data base which will allow for the retrospective and prospective collection and review of clinical data and prescription data on HIV infected patients.

PRIOR AND CURRENT PROGRESS
A total of 505 patients have been enrolled in this protocol; 107 during this past year. There have been no serious or unexpected adverse reactions. Currently, data is being collected for a phase of the study that is looking at zidovudine usage; patient compliance and associated factors. A total of 154 patients have been used in the collection of this retrospective data, with information collection continuing to complete the analysis. The information gained from this study can be used for patient medication compliance.

CONCLUSIONS
Analysis of the data for zidovudine usage is not complete. The pharmacoepidemiologic study is ongoing.

REPORT DATE: 11/24/92 WORK UNIT # 8817

DETAIL SUMMARY SHEET

TITLE: The Effect of HIV Infection on the Initial Manifestations and Response to Treatment of Syphilis

KEYWORDS: HIV, syphilis, treatment

PRINCIPAL INVESTIGATOR: Johnson, Steven MAJ MC
ASSOCIATES: Hicks, Charles LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Nov 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare current therapy of syphilis with a more intensive regimen in patients with and without HIV infection.

TECHNICAL APPROACH
Randomized double-blind placebo-controlled comparison of two antibiotic treatment regimens for HIV-infected patients with syphilis.

PRIOR AND CURRENT PROGRESS
This is a CDC-sponsored multi-center trial. At WRAMC, 10 patients have been enrolled since January 1991; four of them during calendar year 1992. Nationally, the trial has enrolled approximately 350 patients. The goal of 600 study patients nationwide should be reached by the end of 1993, when recruitment will end. The study will continue with follow-ups through the end of 1994. No interim study results are available at the current time.

CONCLUSIONS
There are no study results yet. However, this remains a landmark study on syphilis treatment in HIV infection.

REPORT DATE: 06/29/93 WORK UNIT # 8818

DETAIL SUMMARY SHEET

TITLE: Prospective Study of the Emergence of Zidovudine Resistance in Patients Infected with the Human Immunodeficiency Virus who are Treated with Zidovudine

KEYWORDS: AZT resistance, virus culture, HIV

PRINCIPAL INVESTIGATOR: Mayers, Douglas CDR MC
ASSOCIATES: Oster, Charles COL MC; Wagner, Kenneth MD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if there exists a level of AZT resistance, measured in vitro, which correlates with clinical deterioration in patients receiving AZT. Secondarily, to determine the time course, frequency and clinical parameters associated with development of AZT resistance, and to develop a repository of HIV-infected PBMC and plasma for future studies of AZT resistance.

TECHNICAL APPROACH
HIV-infected patients taking AZT will be clinically evaluated every 3 months. Blood will be drawn at each evaluation for HIV-culture, p24Ag, T cell subsets, and AZT levels. Aliquots of PBMC and plasma will be stored in liquid nitrogen. HIV isolates will be evaluated for susceptibility to AZT, DDC, and DDL. Genotypic analysis of the HIV reverse transcriptase gene will be performed on selected patient isolates. Primary clinical endpoints are death or development of a new opportunistic infection. Data will be evaluated using a Mantel-Haenszel survival analysis with transition states.

PRIOR AND CURRENT PROGRESS
The study closed to accrual in late 1991 with 100 patients. To date, there have been 19 deaths, 38 opportunistic infection primary study endpoints, 32 episodes of oral candidiasis, 42 with CD4 decline below 200 CD4 cells, 25 developed anergy, and 14 developed wasting. Sixteen patients withdrew prior to completion of the protocol, and 30 patients have completed the 2-year study. Eighteen patients have signed up for a 1-year extension of follow-up. Of the 60 patients who entered the study with AZT-sensitive virus, 34 continue to have AZT-sensitive virus, and 26 have developed AZT-resistant virus.

CONCLUSIONS
Factors which predict early development of AZT resistance include: low CD4 count at initiation of therapy, p24 antigen positive status, and presence of a syncytium-inducing (SI) HIV isolate. Patients with AZT-sensitive virus maintain stable CD4 counts for up to 3-4 years. CD4 cell counts decline by 50% during the year that AZT resistance develops.

REPORT DATE: 09/21/93 WORK UNIT # 8819

DETAIL SUMMARY SHEET

TITLE: Active Immunization of Early HIV Infected Patients with Recombinant GP160 HIV Protein: Phase II Study of Toxicity, Immunotherapy, In Vivo Immunoregulation and Clinical Efficacy

KEYWORDS: rgp160, HIV infection, vaccine therapy

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy of recombinant gp160 (rgp160) in the treatment of patients with early HIV infection.

TECHNICAL APPROACH
This placebo-controlled, double-blind Phase II study will consist of 600 patients overall: 300 to be enrolled within the Department of Defense and 300 to be enrolled in sponsor supported civilian sites. Patients will be equally randomized to vaccine or placebo. All volunteers will receive intramuscular injections of 160 ug on days 0, 7, 30, 60, 120, 180 and then at 2 month intervals through the completion of the trial. Changes in cellular and humoral immune responses, toxicity to rgp160, changes in CD4 counts, and shifts in viral burden will all be explored.

PRIOR AND CURRENT PROGRESS
This multi-center trial involves 17 study sites. A total of 608 volunteers were randomized to receive rgp160 or placebo; 130 during the past year. WRAMC has entered 93 volunteers; 17 during the past year. Enrollment was closed in November 1992. Seven volunteers discontinued the trial. Three deaths have occurred; two HIV related (both WRAMC volunteers August 1993) and one suicide (non-WRAMC site). Overall, 37 primary endpoints and 109 secondary endpoints have occurred. A summary of cumulative adverse events and study events are attached (attachment 3). Three lymphomas have occurred; all at WRAMC. Studywide, 39 of the volunteers are receiving AZT, 8 DDI, and 1 DDC.

CONCLUSIONS
This project is ongoing; the projected completion date is November 1995. Protocol integrity continues to be maintained. Since the trial remains double-blinded, minimal conclusions can be drawn at this time. Progress is monitored by an independent DSMB. The initial efficacy analysis will be conducted using all data available through September 1993; DSMB review is scheduled for December 1993.

REPORT DATE: 09/20/93 WORK UNIT # 8820

DETAIL SUMMARY SHEET

TITLE: A Phase I Study of the Safety and Immunogenicity of rgp120/HIV-1-111B Vaccine in HIV-1 Seropositive Adult Volunteers

KEYWORDS: gp120, vaccine therapy, HIV infection

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the safety and immunogencitiy of rgp120 vaccine in asymptomatic HIV-1 infected volunteers, compare the effectiveness of a 3-injection vs. 5-injection schedule, and compare the effect of variable dose levels of rgp120 vaccine.

TECHNICAL APPROACH
This Phase I trial will consist of four groups: three open label (100, 300, 600 ug), with 5-10 patients each; and one placebo controlled (20 300 ug vaccine, 5 placebo). All volunteers will be vaccinated at 0, 1, 4, 8, 16 weeks. Alterations in cellular and humoral immune response to HIV specific proteins and changes in vivo and in vitro cellular immune function will be assessed. The continuation trial consists of four groups (all open label). Groups as follows: 300 ug q 1 month (15 volunteers); 300 ug q 3 months (15 patients); 600 ug q 3 months (10 volunteers); and 600 ug per original schedule (initial trial placebos).

PRIOR AND CURRENT PROGRESS
The continuation trial enrolled 41 of the original volunteers (none this past year). Group 8 enrolled 14 (300 ug q 1 month); group 9 enrolled 14 (300 ug q 3 months); and group 12 enrolled 9 (600 ug q 3 months). Four of the original placebo recipients (Group 11) received 600 ug immunization series per original schedule . To date, 38 volunteers have completed the extended immunization protocol; 1 volunteer discontinued prior to protocol completion. To date, two volunteers have developed PCP, and one developed thrush. Four have developed CD4 cell counts less than 200. Nine have received antiretroviral therapy (AZT/DDI) per primary physician. Comparative analysis of immunogenicity by group is in progress and should be completed by the end of this year.

CONCLUSIONS
This trial is ongoing; extended trial will be completed by November. Although preliminary data demonstrated a dose response curve for immunogenicity, 600 ug appears to be more optimal in terms of immunogenicity. Volunteers which meet specific protocol criteria will be allowed to enroll and continue immunization consiting of 600 ug q 2 months for 12 additional months.

REPORT DATE: 11/10/92 WORK UNIT # 8824

DETAIL SUMMARY SHEET

TITLE: Phase I Study of Alferon N Injection in Persons with Asymptomatic Human Immunodeficiency Virus (HIV) Infection

KEYWORDS: interferon, HIV, AIDS

PRINCIPAL INVESTIGATOR: Skillman, Donald MAJ MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the safety and tolerance of natural interferon alfa-N3 in persons in persons infected with HIV.

TECHNICAL APPROACH
Progressively higher doses of interferon alfa-N3 will be given to a total of 20 persons. The drug is delivered subcutaneously by self-injection on Monday-Wednesday-Friday for an initial 12 week interval. Regular physical examinations and laboratory tests are performed to document the safety and tolerance of the drug.

PRIOR AND CURRENT PROGRESS
No persons were enrolled in this study at WRAMC. Study-wide, 19 volunteers have been enrolled and are either on therapy or have completed therapy at the National Naval Medical Center. There have been no serious or unexpected adverse reactions. The drug has shown remarkably good tolerance and almost no laboratory toxicity. At doses as high as 20 million units, there have been no adverse symptoms at all. The study will be continued only at the National Naval Medical Center. The investigational drug is kept there.

CONCLUSIONS
Interferon alfa-N3 has demonstrated almost no laboratory toxicity and is very well tolerated. As this interferon product has shown in vitro superiority when compared to recombinant interferon alphas for anti-HIV activity, further investigation of its potential as an anti-retroviral agent is warranted.

REPORT DATE: 10/14/92 WORK UNIT # 8825

DETAIL SUMMARY SHEET

TITLE: Role of Accessory Cells in Hematopoietic Suppression After HIV-Infection

KEYWORDS: HIV-1, bone marrow, myelopoiesis

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC
ASSOCIATES: Schwartz, Gretchen PhD; Oster, Charles COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study whether the decreased numbers of mature blood cells seen in HIV-infected people relate to decreased production of bone marrow progenitor cells that produce the blood cells, abnormal responses of the progenitor cells to growth factors, or impaired production of growth inhibitory and growth stimulatory cytokines from accessory cells in the bone marrow microenvironment that regulates the production of mature blood cells and their progenitor cells.

TECHNICAL APPROACH

Human bone marrow long-term cultures (LTC) will be used to study how HIV-infected accessory cells effect production of mature blood cells and their progenitor cells. The stromal cell layer (an adherent layer of cells that forms in LTC) is used to simulate the bone marrow microenvironment. Stromal cells layers are begun by culturing bone marrow of noninfected people for 4 weeks, and then infecting the layers with HIV-1. Autologous CD34+ marrow cells, enriched for primitive cells that produce progenitor cells for mature blood cells, are added to the infected stromal cell layers. The effect of HIV-infection on myeloid and erythroid progenitor cell production is monitored by colony-forming assays.

PRIOR AND CURRENT PROGRESS

Bone marrow is from W.U. #9022-83. A reproducible, productive 0.5 ml bone marrow LTC system was devised. Some LTC stroma cell layer cells were targets for HIV-1 ADA (a monocytotropic strain of HIV-1). A productive infection was maintained for at least 8 wks in HIV-infected stromal cell layers; within 1 wk, 50-70% fewer progenitor cells were produced in HIV-infected LTC than in noninfected LTC. In preliminary studies, addition of G-CSF did not further stimulate progenitor cell production; production, however, was increased when neutralizing antibodies to TNF-alpha or IL-4 were added to HIV-infected LTC.

CONCLUSIONS

Results suggest that HIV-infected bone marrow accessory cells suppress production of erythroid and myeloid progenitor cells that produce mature blood cells and that this may be mediated by growth inhibitory cytokines. The small LTC system developed provides a reproducible system with replicates that may help identify therapeutic strategies to overcome/prevent severe hematopoietic suppressions that develop with AIDS.

REPORT DATE: 08/05/93 WORK UNIT # 8826

DETAIL SUMMARY SHEET

TITLE: A Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study of the Use of Weekly Azithromycin as Prophylaxis Against the Development of Mycobactrium avium Complex Disease in HIV Infected People

KEYWORDS: azithromycin

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test the hypothesis that Mycobacterium avium complex disease can be prevented in late stage HIV disease by the use of azithromycin once a week.

TECHNICAL APPROACH
This is a multi-center placebo controlled study, in which volunteers with HIV and T helper cell counts below 100 receive either placebo or azithromycin once a week. The patients are monitored monthly for symptoms, signs, and laboratory findings suggestive of or diagnostic of Mycobacterium avium infection.

PRIOR AND CURRENT PROGRESS
A total of 52 patients have been enrolled in this study from all participating centers. Since February 1993, 13 patients have been enrolled from WRAMC. Only 12 of the 13 have received the drug/placebo, because one had a clinical syndrome consistent with MAC infection immediately prior to the first month of preventive therapy. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
There are no conclusions at this point in the study.

REPORT DATE: 09/02/93 WORK UNIT # 8827

DETAIL SUMMARY SHEET

TITLE: Active Immunization of AZT-Treated HIV-Infected Patients with Recombinant GP160 HIV Protein: Phase I/II Study of Immunogenicity Toxicity, and Effect in In Vivo Immunoregulation

KEYWORDS: HIV infection, vaccine therapy, gp160 vaccine

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To conduct a Phase I/II trial of the recombinant human immunodeficiency virus (HIV) envelope glycoprotein, gp160 candidate vaccine in patients who are HIV infected (Walter Reed Stage 1-2). Specific objectives include: 1) to evaluate the immunogenicity and toxicity of this product in HIV-infected individuals on AZT; and 2) to determine the parameters predictive of immune responsiveness.

TECHNICAL APPROACH

This is a multi-center, tri-service HIV research protocol conducted at Walter Reed Army Medical Center, National Naval Medical Center, and Wilford Hall Medical Center within the Military Medical Consortium for Applied Retroviral Research. Volunteers initially have HIV infection stage WR1-2. They will receive AZT (at least 500 mg/day for 12 weeks) statified by baseline CD4 count, and then 160 ug intramuscular injections of this vaccine on days 0 and 7, and at months 1, 2, 4, 6, and 10. Safety parameters, adaptive anti-HIV immune responses, and parameters of HIV in vivo regulation will be monitored. Volunteers will be eligible for standard of care intervention under the direction of their physicians.

PRIOR AND CURRENT PROGRESS

Altogether, 78 volunteers were enrolled in this study; 64 were randomized and vaccinated. WRAMC enrolled 37 of the total volunteers; 29 were randomized and immunized. Enrollment was closed in April 1993. To date, toxicity has been limited to local reactions; all adverse reactions filed with Wyeth-Ayerst were considered not vaccine related. Preliminary analysis of immunogenicity data is limited to T cell proliferative responses, which although not statistically distinct suggest a trend toward decreased immunogencity in volunteers with CD4 cell counts less than 300.

CONCLUSIONS

This trial is ongoing. Although preliminary data suggest limitations related to cellular immunogencity in volunteers with advanced CD4 depletion (counts <300), confirmation awaits trial completion and final analysis (summer 1994).

REPORT DATE: 08/12/93 WORK UNIT # 8100

DETAIL SUMMARY SHEET

TITLE: Serum Penicillin Levels Following Intramuscular Injection of Benzathine Penicillin

KEYWORDS: benzathine penicillin, serum penicillin levels

PRINCIPAL INVESTIGATOR: Ames, William CPT AN

SERVICE: Ireland Army Hospital, Fort Knox, Ki STATUS: Completed
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study penicillin levels in serum of basic-training military personnel from 1 to 29 days after injection of benzathine penicillin.

TECHNICAI APPROACH
All trainees will be administered IM bicillin on the same day. Blood serum levels will be drawn on each trainee on days 1, 8, 15, 22, and 29 after the bicillin is administered. The serum will be centrifuged, decanted, and then stored at the blood bank at -85 degrees C.

PRIOR AND CURRENT PROGRESS
During the first year of this study, 71 trainees were enrolled. Each subject received IM bicillin on the same day. After administration of the drug, blood was drawn on days 1, 8, 15, 22, and 29 (during July-August 1992). The serum samples are presently being stored in a freezer at -85 degrees C until a testing lab is found. There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Use of humans in this research has been completed.

REPORT DATE: 02/12/93 WORK UNIT # 1502

DETAIL SUMMARY SHEET

TITLE: CALGB 8945: A Phase II Study of Toremifene in Metastatic Breast Cancer

KEYWORDS: breast cancer, metastatic, anti-hormones

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the objective response rate of Toremifene in patients with mestastatic breast cancer who are ER and PgR negative. To evaluate duration of response, time to progression, and survival; and to assess the toxicities of Toremifene.

TECHNICAL APPROACH
All eligible patients will be assigned the same dose of oral Toremifene, 200 mg twice/day. Treatment will continue until disease progresses or toxicity occurs. Close monitoring for toxicities will be maintained.

PRIOR AND CURRENT PROGRESS
This study was suspended for accrual in December 1991. It officially closed August 28, 1992. Two patients from WRAMC were entered on this study; the latest one was from November 1991. No patients were entered during this reporting period. The two patients from WRAMC experienced no adverse effects. They both were removed from the study due to progressive disease. Both are still alive and receiving other therapy. Several suspected adverse reactions have been reported from the drug company and reviewed by the WRAMC IRB. The total accrual for this study from CALGB was 21 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/22/93 WORK UNIT # 1504

DETAIL SUMMARY SHEET

TITLE: CALGB 8662 Monitoring Circulating Breast Cancer Associated Antigens with the 15-3 Radioimmunoassay in Metastatic Breast Cancer

KEYWORDS: metastatic breast cancer, CA15-3 antigens

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the predictive value of a given change in CA15-3 values related to a known clinical event (response, progression or stability)

TECHNICAL APPROACH
Ten cc of whole blood is drawn at the time of study entry, at each follow-up visit, and at the time of relapse or disease progression. The plasma is mailed on dry ice to the referenced laboratory

PRIOR AND CURRENT PROGRESS
A total of 21 patients from WRAMC have been entered on this study; 5 were entered during this reporting period. The total national accrual is 338, with a projected accrual of 400 patients. Blood samples continue to be obtained on all patients at the specified time points. No patients have been withdrawn. No adverse reactions have occurred.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 02/12/93 WORK UNIT # 1505

DETAIL SUMMARY SHEET

TITLE: CALGB 8963 Psychological Adaptation of Survivors of Acute Leukemia

KEYWORDS: psychosocial adaptation, survivors, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the long-term psychological impact of a devastating disease, such as acute leukemia, and the impact of surviving treatment.

TECHNICAL APPROACH
The patient has one phone interview and completes one questionnaire from the Department of Psychiatry at Memorial Sloan-Kettering.

PRIOR AND CURRENT PROGRESS
A total of 11 patients from WRAMC have been entered on this study; the latest one in February 1991. No patients were entered during this reporting period. All interviews have been completed. No patients refused to participate after initial consent. This is considered a low risk study; no adverse effects have been seen. The total national accrual, to date, is 146. The projected accrual is for 200 patients.

CONCLUSIONS
Analysis is ongoing; no conclusions have been reached.

REPORT DATE: 03/03/93 WORK UNIT # 1506

DETAIL SUMMARY SHEET

TITLE: CALGB 8922 Interleukin-2 in Acute Myelogenous Leukemia

KEYWORDS: AML, second remission, interleukin-2

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the activity of interleukin-2 (IL-2) in prolonging remission in acute myelogenous leukemia (AML) patients who are in second remission. To monitor the effect of IL-2 on display.

TECHNICAL APPROACH
Patients will be randomized to receive or not receive IL-2. If IL-2 is received, it will be given IV by constant infusion 5 days every 2 weeks for 2 months. Blood samples will be drawn before, during, and after treatment. Samples will be drawn twice on patients who do not receive IL-2.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered into this study. The study was opened in February 1990 and was suspended to patient accrual in November 1990. The study officially closed August 24, 1992. Oncology group coordinators never published a report on this study; therefore, no information about groupwide enrollment or unexpected/adverse reactions can be reported.

CONCLUSIONS
Analysis is in progress.

REPORT DATE: 11/05/92 WORK UNIT # 1509

DETAIL SUMMARY SHEET

TITLE: CALGB 9011 A Study of Fludarabine Vs. Chlorambucil Vs. Both Drugs for Chronic Lymphatic Leukemia

KEYWORDS: fludarabine, chlorambucil, crossover therapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the response rates and progression free survival in previously untreated chronic lymphatic leukemia (CLL) patients using three therapeutic regimens; to determine whether the quality of life is superior in any one of the regimens; to determine whether the two drugs fludarabine and chlorambucil, are non-resistant by a crossover design for patients failing to respond to the initial single agent.

TECHNICAL APPROACH

Randomized study for eligible CLL patients comparing the new drug fludarabine with the standard treatment of chlorambucil, or with the two drugs given in combination. Length of treatment depends on patient's response, with the maximum treatment being 2 years. Fludarabine is given intravenously for 5 days every 28 days. Chlorambucil is given by mouth for 1 day every 28 days.

PRIOR AND CURRENT PROGRESS

One patient from WRAMC has been entered on this study. No patients have been entered during this reporting period. The one patient completed six cycles of fludarabine and achieved a complete remission. No unexpected toxicities were obse ved. The primary toxicity was neutropenia which continued for approximately 3 months post treatment. The benefit obtained was a complete response. No patients have been withdrawn from the study. As of March 1992, 129 patients have been entered nationwide. The projected accrual is for 450 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 11/05/92 WORK UNIT # 1510

DETAIL SUMMARY SHEET

TITLE: CALGB 9051 A Study of Combination Chemotherapy Plus Irradiation for Early Stage Hodgkin's Disease

KEYWORDS: poor risk Hodgkin's, limited chemotherapy, subtotal nodal radiation

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To establish the response rate to three cycles of EVA and radiation therapy in untreated patients with early stage, poor risk Hodgkin's disease. To establish the short and long term complications of combined therapy. To assess patterns of failure, relapse rate, disease-free survival and overall survival in patients treated with EVA and subtotal nodal irradiation.

TECHNICAL APPROACH
All eligible patients will receive three cycles of chemotherapy at 28 day intervals consisting of VP-16, vinblastine, and doxorubicin. This will be followed by a total of 39 radiation treatments given with a 4 week break in between.

PRIOR AND CURRENT PROGRESS
A total of four patients from WRAMC have been entered on this study; two during this reporting period. No unexpected adverse reactions have been observed. No patients have withdrawn. The two initial patients are in complete remission and are being followed at WRAMC. The latter two are just completing their radiation. The study reached its accrual goal in June 1992 and is now closed to further patient registration.

CONCLUSIONS
The data is being analyzed. No conclusions have been reached.

REPORT DATE: 11/05/92 WORK UNIT # 1511

DETAIL SUMMARY SHEET

TITLE: CALGB 9081: An Intergroup Study of Rectal Cancer Adjuvant Therapy

KEYWORDS: adjuvant chemotherapy, post-op radiation, poor prognosis

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of: (1) 5FU, (2) 5FU and leucovorin, (3) 5FU and levamisole, and (4) 5FU, leucovorin, and levamisole when combined with pelvic radiation therapy in the treatment of Stages B-2 and C rectal cancer.

TECHNICAL APPROACH
This is a four-armed study with the same radiation therapy program in all arms, but with varying drug regimens. All eligible patients will be randomized to receive one of four treatment arms with 5FU and radiation being the control arm of the study. All arms receive two courses of chemotherapy, radiation therapy along with two courses of chemotherapy, and then two additional courses of chemotherapy.

PRIOR AND CURRENT PROGRESS
A total of six patients from WRAMC have been entered on this study. Two of those patients have been entered this reporting period. No unexpected toxicities have been observed from any of the treatment arms. No patients have withdrawn from the study. None of these patients have had recurrence of their cancer. This study will be closed to new patient accrual November 1992. We will continue to follow the six patients for recurrence.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 12/15/92 WORK UNIT # 1513

DETAIL SUMMARY SHEET

TITLE: CALGB 8923 Randomized Studies of Induction Therapy Adjuncts and Intensification Therapy Regimens for Older Patients with Acute Myelocytic Leukemia

KEYWORDS: AML, over age 60, growth factors

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the effect of GM-CSF on the rates of complete remissions (CR) and hypoplastic deaths in elderly patients treated with daunorubicin and Ara-C induction therapy; to compare the incidence of infections, time to bone marrow recovery with GM-CSF vs. placebo; to determine the incidence and significance of leukemic regrowth using GM-CSF; and to determine the efficacy of two different post-remission intensification therapies in prolonging disease-free survival.

TECHNICAL APPROACH

All eligible patients over age 60 will be randomized to receive standard Ara-C and daunorubicin with blinded study drug of GM-CSF or placebo. Those patients who attain a CR after induction are randomized again to receive an intensification of four additional courses of Ara-C or two courses of Ara-C/mitoxantrone.

PRIOR AND CURRENT PROGRESS

Two patients from WRAMC have been entered on this study; none during the past year. Both patients have been removed from the study; one for progressive disease and the other for progressive disease following 10 months of cytopenia. The former patient died of the disease; the second patient is being followed for survival. No unexpected toxicities have been observed. No patients have been withdrawn for reasons other than disease progression. A total of 257 patients have been entered nationwide; 97 during the past year. The projected accrual is for 384 patients.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 12/15/92 WORK UNIT # 1514

DETAIL SUMMARY SHEET

TITLE: CALGB 9021 Induction Therapy for Relapsed or Refractory Acute Myelocytic Leukemia or Blast Crisis of Chronic Myelocytic Leukemia

KEYWORDS: AML/CML, induction study, growth factor priming

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare response rates of patients with refractory or relapsed acute myelocytic leukemia (AML) and untreated blast crisis of chronic myelocytic leukemia (CML) treated with GM-CSF plus high dose cytarabine to high dose cytarabine alone; to evaluate the toxicity of high dose cytarabine alone and with GM-CSF added; to evaluate in vivo and in vitro effects of GM-CSF on leukemic blood and bone marrow; and to correlate patient response with in vitro studies of the cells.

TECHNICAL APPROACH

This is a study of induction therapy alone. Eligible patients with relapsed or refractory AML or untreated blast crisis of CML will be randomized to receive IV GM-CSF vs placebo 2-5 days before, during, and 24 hours after high dose Ara-C induction therapy. If a complete remission is not achieved, a second induction will be given. Bone marrow and blood samples will be obtained before and after GM-CSF and at specified intervals thereafter. Responders are monitored until relapse.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. A total of 84 patients have been entered nationwide; 55 this past year. The projected accrual is for 282 AML patients and 98 CML patients. There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 10/15/92 WORK UNIT # 1516-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8364: Immunological Diagnostic Studies in Adult ALL

KEYWORDS: immunology, lymphocyte, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of various monoclonal antibodies' cytochemical and conventional lymphoid markers in adult acute lymphatic leukemia (ALL). To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease, response rate, and response duration. To determine if marker status changes at relapse.

TECHNICAL APPROACH
Non-randomized study in which all eligible patients being entered on the ALL treatment protocol agree to allow prior to the initiation of therapy the submission of six air-dried unstained BM smears for confirmatory cytochemical studies and 2cc of bone marrow aspirate, along with 7 cc of peripheral blood to a designated CALGB reference laboratory. The same set of samples is again obtained at relapse.

PRIOR AND CURRENT PROGRESS
This study opened in June 1983 as a companion to ALL treatment studies. A total of 25 patients have been entered from WRAMC; 3 of those since the last reporting period. Fourteen patients have died; 11 patients continue to be followed for relapse. No adverse effects have been noted from the blood or bone marrow sampling. No benefit to the patients has been cited. A total of 570 patients have been entered nationwide.

CONCLUSIONS
Study is ongoing. No conclusions have been reached.

REPORT DATE: 02/12/93 WORK UNIT # 1517

DETAIL SUMMARY SHEET

TITLE: CALGB 9013: Alpha Interferon and Cytarabine for Untreated Chronic Myelogenous Leukemia

KEYWORDS: untreated CML, Philadelphia chromosome

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether the combination of low dose Ara-C and alpha interferon (IFN) can reduce or eliminate the Ph + cells in previously untreated patients with chronic phase chronic myelogenous leukemia (CML); to assess response rate, duration of response, and survival of patients with CML treated with this regimen; to define safety and toxicities of this treatment; and to investigate concordance of Ph - and Ph + cells between blood and bone marrow as remission is achieved.

TECHNICAL APPROACH

All eligible patients will have blood and bone marrow samples sent for cytogenetic analysis. Only Ph + patients will be eligible. Blood and bone marrow samples will be repeated at 6 month intervals. Eligible patients will be started on subcutaneous injections of Ara-C twice per day, and subcutaneous injections of alpha IFN daily. Blood counts will be obtained weekly and the doses adjusted according to results. Complete or partial responders will be treated for a total of 18 months. Patients with stable disease will receive 12 months of treatment.

PRIOR AND CURRENT PROGRESS

A total of 56 patients nationwide have been entered on this study; 32 during this past year. No patients from WRAMC have been entered. The projected accrual is for approximately 80 patients. No reports of adverse reactions from the otherinstitutions have been received.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 02/12/93 WORK UNIT # 1518

DETAIL SUMMARY SHEET

TITLE: CALGB 8761: Prognostic Implications of Chromosomal Abnormalities in Chronic Myelogenous Leukemia

KEYWORDS: companion study, CML

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the chromosome 22 translocation breakpoint for previously untreated chronic myelogenous leukemia (CML) patients; to determine the correlation between the breakpoint and patient characteristics at presentation, during clinical course, and at time of blast crisis; and to determine by sequential samples whether breakpoint location changes during the course of the disease or at time of progression.

TECHNICAL APPROACH

Bone marrow samples (2 ml) and blood samples (40 ml) are obtained prior to treatment, after second treatment cycle, and every 6 months thereafter. Samples are also obtained during blast crisis. The samples are mailed to the reference lab for analysis. These samples are obtained during regularly scheduled blood and bone marrow sampling required for treatment.

PRIOR AND CURRENT PROGRESS

This study is a companion to the treatment study for CML. No patients from WRAMC have been entered on this study or the treatment study. The total national accrual, to date, is 121; 32 during the past year. The projected accrual is for 200 patients. No reports of adverse reactions from the other institutions have been received.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 03/12/93 WORK UNIT # 1519

DETAIL SUMMARY SHEET

TITLE: CALGB 9142 Comparison of Chemotherapy Vs. Chemohormonotherapy in Premenopausal Women with Stage II Receptor Positive Breast Cancer

KEYWORDS: breast cancer, node positive, receptor positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the recurrence rates, disease-free intervals, and hormone receptor positive survival for premenopausal women with lymph node positive breast cancer given adjuvant therapy with cytoxan, Adriamycin, and 5-fluorouracil (CAF) chemotherapy alone, or chemotherapy followed by zoladex, or chemotherapy followed by zoladex and tamoxifen. To compare the relative toxicities of these three regimens, and to assess their effect on blood hormone levels.

TECHNICAL APPROACH

All eligible patients will receive a 6 month course (six cycles) of standard CAF therapy. Initially, they will be randomized to receive an additional 5 years of zoladex, receive an additional 5 years of zoladex and tamoxifen, or end therapy following CAF.

PRIOR AND CURRENT PROGRESS

A total of nine patients from WRAMC have been entered on this study. Two of those were entered during this reporting period and are still receiving chemotherapy. No adverse reactions have been observed. The remaining seven patients are still being followed for evidence of recurrence. No patients have withdrawn from the study. A total of 850 patients have been entered nationwide. The projected accrual is for 1500 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 03/12/93 WORK UNIT # 1520

DETAIL SUMMARY SHEET

TITLE: CALGB 9143 Comparison of Combination Chemotherapy with the CAF Regimen Vs. A 16-week 6-Drug Regimen for Stage II Receptor Negative Breast Cancer

KEYWORDS: breast cancer, adjuvant therapy, node positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare disease-free and overall survival in node-positive, receptor-negative breast cancer patients receiving adjuvant cytoxan, Adriamycin, and 5-fluorouracil comcomitantly (CAF) or a 16-week multi-drug regimen. To compare toxicities of adjuvant CAF and a 16 week multi-drug regimen.

TECHNICAL APPROACH
Eligible patients are randomized to receive either six 28-day courses of CAF or the 16-week multi-drug regimen. If randomly assigned to the second treatment, a central venous catheter is inserted prior to treatment.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered on this study. A total of 48 patients have been entered nationwide. The projected accrual is for 630 patients. The latest CALGB review reports 53% of the evaluable patients had grade 4 toxicities, primarily hematologic. No unexpected toxicities were observed. The toxicities · re slightly higher in the multi-drug treatment arm.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 04/16/93 WORK UNIT # 1521-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9194: Comparison of Adjuvant Chemotherapy with Concurrent or Delayed Tamoxifen vs. Tamoxifen Alone in Postmenopausal Patients with Receptor Positive Stage II Breast Cancer

KEYWORDS: postmenopausal, lymph node positive, receptor positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen and/or progesterone receptors treated with standard adjuvant therapy with long-term tamoxifen, or with chemoendocrine therapy with combined cytoxan, Adriamycin, and 5-fluorouracil (CAF) followed by long-term tamoxifen, or with concurrent chemoendocrine therapy with tamoxifen and CAF.

TECHNICAL APPROACH

Eligible patients will be randomized to receive one of three treatment arms: tamoxifen alone for 5 years, six courses of CAF followed by tamoxifen for 5 years, or six courses of CAF with concurrent tamoxifen for 5 years.

PRIOR AND CURRENT PROGRESS

This study opened April 1991. A total of two patients from WRAMC have been entered; both within the past month. One patient is receiving CAF with concurrent tamoxifen. The other patient was assigned tamoxifen alone. No unexpected toxicities have been observed. No patients have been withdrawn from the study. The total national accrual is 89; 35 of those were registered during this reporting period. The projected national accrual is for 1,410 patients.

CONCLUSIONS

None. Analysis is ongoing.

REPORT DATE: 09/27/93 WORK UNIT # 1522-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8461: Cytogenic Studies in Acute Leukemia: A Companion to CALGB 8011, 8323, 8321, and 8411

KEYWORDS: cytogenetics, acute leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Sep 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of specific chromosome abnormalities in adult acute non-lymphatic leukemia (ANLL) and acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
All eligible patients are registered to this companion to treatment protocols. A specimen of marrow and blood is obtained at diagnosis and again at relapse.

PRIOR AND CURRENT PROGRESS
The total national accrual is approximately 2,300 patients; with approximately 350 of those entered this reporting period. A total of 75 patients from WRAMC have been entered on this study; 6 were entered during this reporting period. Relapse samples continue to be sent, as appropriate. No adverse events have occurred. No patients have withdrawn from the study.

CONCLUSIONS
Analysis is ongoing. Projected accrual is to continue until 1998.

REPORT DATE: 04/16/93 WORK UNIT # 1522-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9064: Analysis of Neuroendocrine Markers on Tissue Blocks in Patients with Stage IIIA Non-Small Cell Lung Cancer

KEYWORDS: tissue blocks, retrospective analysis

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To analyze pathology specimens before and after chemotherapy for neuroendocrine markers, carcinoembryonic antigen (CEA), and p185neu to determine if correlation exists between response and/or survival with these markers. To compare pre and post chemotherapy specimens for intensity and percentage of cells positive for neuroendocrine markers, CEA, and p185neu. To correlate light microscopic characteristics with neuroendocrine markers, CEA, p185neu, and clinical parameters.

TECHNICAL APPROACH

Patients must first be registered on the treatment study CALGB 8935. The patient is then registered for this companion study. Tissue blocks are mailed to the reference laboratory for analysis. At completion of the review, tissue blocks will be returned to WRAMC.

PRIOR AND CURRENT PROGRESS

WRAMC participation in this study has been completed. Three patients from WRAMC were treated on CALGB 8935. Tissue blocks on all three patients were sent for analysis, and all three patients have subsequently died of their disease. This study consisted of pathology analysis only; there were no risks to the patients. A total of 40 patients have been entered nationwide; 24 of those during this reporting period. The WRAMC patients were entered during 1991; none during this reporting period. The study is now completed.

CONCLUSIONS

Analysis is ongoing.

REPORT DATE: 01/22/93 WORK UNIT # 1525-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9130: A Trial of Chemotherapy and Radiation with or Without Carboplatin for Inoperable Lung Cancer

KEYWORDS: lung cancer, chemotherapy, radiation therapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if the concurrent addition of carboplatin during radiation therapy for Stage IIIA and IIIB inoperable, non-small cell lung cancer will prolong survival and improve local disease control; to determine if the improvement in survival, if any, is related to disease stage: tumor (T) status and nodal status; and to determine if the improvement in survival, if any, is related to tumor size.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of two treatments: (1) chemotherapy and vinblastine weekly x5, with cisplatin given on the first and last week (a 3 week rest period will be given, followed by a 6 week course of radiation therapy); or (2) the same treatment as #1, with the addition of the drug carboplatin given on the first treatment day of the week during radiation. The total treatment time for both would be 4-5 months.

PRIOR AND CURRENT PROGRESS

One patient from WRAMC has been entered on this study. This patient has achieved a partial response to the disease. No serious or unexpected adverse reactions have been observed. No patients were enrolled and then withdrawn. The total national accrual is 68, with a total projected accrual of 270 pateints.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 01/14/93 WORK UNIT # 1526-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9140: A Phase III Study of CAF-Leucovorin vs. *CAF for Visceral Crisis Breast Cancer

KEYWORDS: metastatic disease, chemotherapy, leucovorin

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the response rates, duration of response, time to treatment failure, and survival of patients with metastatic breast cancer treated with cytoxan, Adriamycin, and 5-fluorouracil (CAF) versus patients treated with CAF plus leucovorin; and to compare the toxicity experienced by the two treatment groups.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of two treatment arms: (1) CAF every 3 weeks; or (2) CAF and leucovorin every 21 days. The treatment may continue as long as 1 year.

PRIOR AND CURRENT PROGRESS
Two patients from WRAMC have been enrolled on this study. No serious or unexpected adverse reactions were observed. Both patients were removed from the therapy due to progressive disease; one after four cycles of therapy, and the other after two cycles. No benefit to the patient was determined. The total accrual for this study is 32 patients. The projected accrual is for 240 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/14/93 WORK UNIT # 1527-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9190: A Trial of Postoperative Interferon in Resected High Risk Melanoma

KEYWORDS: high-dose interferon, low-dose interferon, observation

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To establish the efficacy of interferon alfa-2b as an adjuvant in increasing the disease-free survival and overall survival in patients at high risk for recurrence after definitive surgery for deep primary lesions or after regional lymph node recurrence.

TECHNICAL APPROACH
Eligible patients are randomized to receive one of three treatment plans: (1) high dose interferon for approximately 1 year; (2) low-dose interferon for approximately 2 years; or (3) observation only - frequent follow-up for 2 years, then annually. Those patients randomized to receive interferon will be trained to self-administer their subcutaneous injections at home.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered on this study thus far. The total CALGB accrual is 27. The projected accrual is for 498 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/14/93 WORK UNIT # 1528-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9195: A Trial of Adjuvant Chemoradiation vs. Observation After Gastric Resection of Adenocarcinoma

KEYWORDS: post gastrectomy, adjuvant therapy, observation

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare overall and disease-free survival between patients treated with gastrectomy only and those treated with gastrectomy plus adjuvant therapy; to compare the incidence and patterns of disease failure between these two groups of patients; and to assess patient tolerance of upper abdominal chemoradiation after gastric resection.

TECHNICAL APPROACH
Eligible patients will be randomized to receive either adjuvant chemoradiation, consisting of five courses of 5-fluorouracil and leucovorin plus one course of radiation, or to observation only. This arm would consist of close observation for symptoms of recurrence over a 2 year period, then annual follow-up thereafter.

PRIOR AND CURRENT PROGRESS
No patients have been enrolled on this study from WRAMC. Those patients referred for evaluation were either ineligible from a surgical recovery standpoint or did not consent. A total of 50 patients have been entered nationwide. The projected accrual is for 350 patients. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 04/16/93 WORK UNIT # 1531-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9160: A Phase III Trial of High Dose Cyclophosphamide With G-CSF With or Without Amifostine

KEYWORDS: solid tumors, no standard therapy, chemoprotective agent

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD, DAC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether the addition of WR-2721 will ameliorate the depth of granulocyte and/or platelet nadirs or the duration of granulocyte and/or platelet nadirs in cancer patients receiving intensive cyclophosphamide combined with granulocyte macrophage colony-stimulating factor (GM-CSF). To determine whether WR-2721 will lessen the clinically significant sequela of intensive cyclophosphamide therapy.

TECHNICAL APPROACH

All eligible patients will receive high dose cyclophosphamide, Mesna, and GM-CSF. They will be randomized to receive or not receive WR-2721 with their treatments. Treatment cycles will be repeated every 15 days. All patients responding with a partial remission or complete remission after four doses can be continued on treatment while they continue to respond.

PRIOR AND CURRENT PROGRESS

This study has been open 12 months. WRAMC has entered a total of four patients. These four have been the only patients registered. The projected accrual for this study is 42. Two of the WRAMC patients were removed from study due to progressive disease; they both have died of their disease. One patient was removed from the study due to toxocity (hematologic) and hypotension (from the WR-2721). The fourth patient has had a partial remission and is still receiving therapy. He is on cycle six and is receiving WR-2721. No unexpected toxicities have been observed. No patients have been withdrawn other than those mentioned previously.

CONCLUSIONS

Analysis is ongoing.

REPORT DATE: 06/16/93 WORK UNIT # 1532-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9261 A Phase I Study of Topotecan and Cisplatin

KEYWORDS: solid tumor, Phase I, topotecan/cisplatin

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define the maximum tolerated dose of cisplatin that can be administered with a fixed dose of topotecan, and to determine the toxicities of the combination.

TECHNICAL APPROACH
All eligible patients, when registered, will be assigned a specific dose of cisplatin and topotecan. There will be three patients per dose level. An evaluation of all patients will be done weekly to determine toxicities. The doses of cisplatin will be escalated with each cohort of three patients until the maximum tolerated dose for that level has been determined.

PRIOR AND CURRENT PROGRESS
A total of 16 patients from WRAMC have been entered on this study. The total national accrual is 26. The dose levels ranged from 1 to 7. Four patients have died of progressive disease, one died of probable coronary disease, five were removed from therapy after they reached their dose limiting toxicity, five were removed due to progressive disease, and one patient continues therapy on the first dose level (since August 1992) with a partial response. No unexpected toxicities have been observed. Grade 3 and 4 hematologic toxicity did occur in all patients. Colony stimulating factors were added to the treatment plan with addendum 5 to overcome this.

CONCLUSIONS
No conclusions have been reached. Analysis is ongoing.

REPORT DATE: 06/15/93 WORK UNIT # 1560-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8642: A Master Protocol to Study Single Agent Chemotherapy Vs. Standard Chemotherapy for Advanced Breast Cancer

KEYWORDS: chemotherapy, cancer, breast

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate single Phase II agents in achieving responses in previously untreated metastatic breast cancer patients.

TECHNICAL APPROACH
Randomized study in which all eligible patients receive either standard cytoxan, Adriamycin, and 5-fluorouracil (CAF) therapy or a Phase II agent. Those randomized to receive a Phase II agent are treated for two cycles, then reevaluated for response or progression. If progression occurs, they are switched to CAF therapy. The next Phase II drug treatment arm, using alsamitrucin, was approved by the CALGB June 1992 for limited institutions.

PRIOR AND CURRENT PROGRESS
The total national accrual to date is 336 patients; 35 registered during this reporting period. The total WRAMC accrual is 17; 7 have died of progressive disease, 3 were removed from treatment due to progressive disease, 2 achieved a comple response and refused further therapy, and 5 remain on therapy. Six WRAMC patients entered the study this reporting period; four of them received alsamitrucin. No unexpected or serious adverse reactions were observed. One patient refused therapy after attaining a complete response after seven cycles, and remains in complete remission.

CONCLUSIONS
No conclusions have been reached. Analysis is ongoing.

REPORT DATE: 10/15/92 WORK UNIT # 1573-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8762: Molecular Subtypes in Acute Lymphatic Leukemia with Philadelphia Chromosome

KEYWORDS: Philadelphia chromosome, ALL

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of pH positivity in patients with previously untreated acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized comparison study in which all eligible patients who consent allow a sample of blood and bone marrow to be sent to a reference laboratory at the time of diagnosis, first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS
A total of six patients from WRAMC have been entered on this study; one patient during this reporting period. One patient was removed from study after a revised diagnosis. The five remaining continue to be followed for relapse. No adverse effects have been noted from blood and bone marrow sampling. No benefit to the patients has been realized. A total of 161 patients have been entered nationwide; 23 during the past year. The projected accrual is 250.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 10/15/92 WORK UNIT # 1574-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia

KEYWORDS: immunoglobulin, T-cell receptor, ALL

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of Ig and T-cell receptor gene rearrangements from samples of patients with previously untreated adult acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized companion study in which all eligible patients who consent allow a sample of bone marrow and blood to be sent to CALGB reference laboratory at the time of diagnosis, prior to first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS
A total of seven patients from WRAMC have been entered on this study; one during this reporting period. Blood and bone marrow samples are being obtained concurrently with the scheduled diagnostic bone marrows. No adverse reactions have occurred. No benefit to the patients has been cited. A total of 195 patients have been entered nationwide; 25 during this reporting period. The projected accrual is 250.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 12/10/92 WORK UNIT # 1577-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (blood drawing phase); previously CALGB 7921): A Comparative Study of 3 Remission Induction Regimens and 2 Maintenance Regimens for AML (treatment phase); previously CALGB 8321

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine the incidence of various markers in acute myelogenous leukemia (AML); b) To correlate the presence of these markers and the surface antigen phenotype they determine with the FAB histological classification; and c) To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease.

TECHNICAL APPROACH

All eligible patients are registered prior to the initial therapy. From the diagnostic bone marrow procedure, 2 cc of bone marrow and 7 cc of peripheral blood are collected and sent by express mail to the CALGB reference laboratory for analysis and confirmation of classification. Samples are again obtained at relapse.

PRIOR AND CURRENT PROGRESS

A total of 60 patients from WRAMC have been entered on this study; one patient was entered this past year. Blood and bone marrow samples were obtained. No serious and/or unexpected adverse reactions have been observed. No benefit to the patient has been noted. No patients have been withdrawn from the study. A total accrual of 1,764 has been reached nationwide; 139 during the past year.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 01/22/93 WORK UNIT # 1579-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8861: Monitoring Circulating Breast Cancer-Associated 15-3 Antigen in Stage II Breast Cancer

KEYWORDS: antigen, breast cancer, Stage II

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine **STATUS**: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the predictive value of rising CA15-3 levels in patients who are clinically free of recurring disease.

TECHNICAL APPROACH

Ten cc of whole blood is collected prior to first therapy, at 28 day intervals during therapy, at 4 month intervals for 2 years, and then every 6 months for 4 years. Blood is processed at WRAMC and shipped to CALGB approved reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS

A total of 14 patients from WRAMC have been entered on this study, with no new patients entered during this reporting period. Blood samples continue to be obtained on follow-up visits. No patients have been withdrawn, and no adverse effects have been observed. The total national accrual for this study is 344; the projected accrual is for up to 750 patients.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT D... 09/27/93 WORK UNIT # 1584-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8896: An Intergroup Study of Adjuvant Therapy of Primary Colon Cancer

KEYWORDS: chemotherapy, adjuvant, colon cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leu... Group B APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare relative toxicity and efficacy of three approaches (low dose leucovorin + 5FU, high dose leucovorin + 5FU, observation) to treatment of patients with Duke's B or C colon cancer post-curative surgery.

TECHNICAL APPROACH

Randomized study in which all eligible patients will be stratified according to extent, obstruction, and metastasis to receive surgery alone, surgery followed by low dose chemotherapy, or high dose chemotherapy.

PRIOR AND CURRENT PROGRESS

A total of approximately 3800 patients were entered nationally; the study closed to new patient accrual July 1992. No new patients were entered this reporting period. A total of 12 patients from WRAMC have been entered on this study. Two WRAMC patients have had recurrence of disease; one has died. The remaining 10 WRAMC patients have completed therapy and continue to be followed. No serious or unexpected adverse reactions have occurred. No patients have been withdrawn from the study.

CONCLUSIONS

The data is being analyzed. No conclusions have been reached. This study should be closed at WRAMC.

REPORT DATE: 01/13/93 WORK UNIT # 1590-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8852: A Study of CHOPE in Diffuse Lymphomas

KEYWORDS: lymphoma, CHOPE, high-dose

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To identify the maximum tolerated dose of cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide (CHOPE) in the treatment of lymphoma, and to assess the safety of giving multiple cycles of high-dose CHOPE therapy.

TECHNICAL APPROACH
Standard doses of CHOPE will be given to the first 20-25 patients enrolled. If tolerated, the doses will be escalated for the next groups sequentially, until the maximum tolerated dose is reached.

PRIOR AND CURRENT PROGRESS
This study opened January 1989. A total of three patients were enrolled from WRAMC during the first year; all subsequently died of their disease. No patients have been enrolled from WRAMC since then. The study was suspended in May 1990, and reopened with escalated doses in January 1992. The addition of granulocyte colony factors was added to the treatment for more rapid recovery of granulocytes.

CONCLUSIONS
Analysis is ongoing; no conclusions have been reached.

REPORT DATE: 04/16/93 WORK UNIT # 1595-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8961 RAS Mutations in Myelodysplasia

KEYWORDS: RAS, oncogenes, myelodysplasia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the prevalance of mutant RAS genes in myelodysplasia. To determine if the presence of such a mutation predicts subsequent leukemic development.

TECHNICAL APPROACH
Non-randomized, non-treatment protocol in which all eligible patients are registered. Blood and bone marrow samples and slides are obtained at entry and again when acute leukemia develops.

PRIOR AND CURRENT PROGRESS
A total of six patients from WRAMC have been entered on this study; two during this reporting period. The total national accrual is 116 patients; 24 of those during this reporting period. This study involves submission of blood and bone marrow samples only. No serious or unexpected adverse reactions have occurred, and no patients have withdrawn their consent. No benefit to the patient has been determined.

CONCLUSIONS
Analysis is going.

REPORT DATE: 08/13/93 WORK UNIT # 1596-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8897 Evaluation of Adjuvant Therapy for Node Negative Primary Breast Cancer, Phase III

KEYWORDS: adjuvant, node negative, breast cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare disease-free survival and overall survival of high risk, primary breast cancer patients with negative axillary lymph nodes treated with standard CMF or CAF chemotherapy. To assess value of the addition of tamoxifen in these patients.

TECHNICAL APPROACH

This is a complicated study in which eligible patients are registered as low, uncertain, or high risk patients. Low risk patients are followed with no therapy. Uncertain risk patients undergo flow cytometry to be categorized as low or high. Those categorized as high risk patients, plus all other known high risks, are then randomized to CMF, CMF with tamoxifen, CAF, or CAF with tamoxifen.

PRIOR AND CURRENT PROGRESS

A total of 34 patients have been entered on this study from WRAMC; 3 were entered during this reporting period. The total national accrual is approximately 4000 patients; 89 of those during this reporting period. No serious or unexpected adverse reactions have been reported. No patients from WRAMC have withdrawn from the study. The study closed to new accrual February 1993. All WRAMC patients have now completed treatment. This study is now being closed. All patients will continue to be followed for relapse.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 08/13/93 WORK UNIT # 1598-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8952 Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III

KEYWORDS: chemotherapy, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare ABVD to the MOPP/ABV hybrid as therapy for patients with Hodgkin's disease in terms of complete response rates, disease-free survival, failure-free survival, and both intermediate and long-term toxicities.

TECHNICAL APPROACH

Randomized study in which eligible patients receive either ABVD or the MOPP/ABV hybrid combination for a minimum of six cycles unless progression is documented.

PRIOR AND CURRENT PROGRESS

A total of six patients from WRAMC have been entered on this study; two of those during this reporting period. A national total accrual of 450 patients has been reported; 82 of those during this reporting period. No adverse or unexpected reactions have been reported. No patients have been withdrawn from the study. The study is ongoing with a projected accrual rate of 900 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 12/14/92 WORK UNIT # 1243

DETAIL SUMMARY SHEET

TITLE: Percutaneous Balloon Valvuloplasty for Patients with Mitral Stenosis or Aortic Stenosis: A Pilot Study

KEYWORDS: valvuloplasty, aortic stenosis, mitral stenosis

PRINCIPAL INVESTIGATOR: Laird, John MAJ MC
ASSOCIATES: Wortham, Dale, COL MC; Prewitt, Kerry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Terminated
APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of percutaneous balloon valvuloplasty (PBV) in adults with aortic or mitral stenosis.

TECHNICAL APPROACH
Symptomatic patients with mitral stenosis and aortic stenosis will be offered PBV as an option to standard surgical valve replacement. PBV will be performed, with immediate and short-term (6 months) hemodynamic, aortographic, and echocardiographic evaluation.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 10/21/92 WORK UNIT # 1260

DETAIL SUMMARY SHEET

TITLE: Antiarrhythmic Therapy in Congestive Heart Failure, VA Cooperative Study #320

KEYWORDS: heart failure, antiarrhythmic therapy, survival

PRINCIPAL INVESTIGATOR: Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the treatment of ventricular arrhythmias with amiodarone prolongs survival by reducing sudden death in patients with congestive heart failure.

TECHNICAL APPROACH
The study is a multicenter, randomized, double-blinded, placebo-controlled trial of the effects of amiodarone on survival in patients with congestive heart failure. Patients qualifying for enrollment must have significant heart failure and ventricular ectopy on ambulatory ECG monitoring. Patients are then randomized to either amiodarone or placebo and then followed for the endpoints of the study. No modifications have been made to the original protocol methods.

PRIOR AND CURRENT PROGRESS
A total of 26 patients have been enrolled in the study from WRAMC; 11 during the past year. Of these 11 patients, 1 has been lost to follow-up, and 1 experienced sudden cardiac death due to ischemia cardiomyopathy due to coronary disease, with ventricular fibrillation noted at the arrest. The researchers remain blinded to the study drug. One patient has had a cardiac arrest with subsequent placement of an AICD and is presently doing well. The remaining patients have shown no serious adverse reactions and are doing well.

CONCLUSIONS
Patients are being actively recruited; the study goal is to recruit three to four more patients at this site.

REPORT DATE: 10/07/92 WORK UNIT # 1264

DETAIL SUMMARY SHEET

TITLE: The Role of Tumor Necrosis Factor After Balloon Angioplasty in a Pig Model

KEYWORDS: TNF, balloon, angioplasty

PRINCIPAL INVESTIGATOR: Carter, Andrew MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 517 Total: $ 517

STUDY OBJECTIVE
To detect the presence of tumor necrosis factor (TNF) in coronary arteries after local injury with balloon angioplasty utilizing immunohistochemical and molecular biologic techniques in the pig model.

TECHNICAL APPROACH
Pigs will undergo coronary angioplasty procedures. Fourteen animals underwent 24 successful procedures. Three deaths occurred (anesthetic - 1; acute procedure - 2) during or within 24 hours of a procedure. Acute procedural complications included; coronary artery rupture (1), and myocardial infarction due to coronary occlusion (1).

PRIOR AND CURRENT PROGRESS
Fourteen animals underwent 24 successful coronary balloon angioplasty procedures. Three deaths occurred (anesthetic - 1; and acute procedure - 2) during or within 24 hours of a procedure. Acute procedural complications included: coronary artery rupture (1); and myocardial infarction due to coronary occlussion (1). Animal procedures are complete. During the past year, immohistochemical staining for TNF at 24 hours and 7 days after balloon angioplasty identified immunoreactive TNF in the media and adventitia of normal coronary arteries from eight pigs, compared with noninjured coronary segments which did not demonstrate immunoreactive TNF (p=.04). Dot assay of injured coronary segments revealed an induction o TNF mRNA 24 hours after balloon angioplasty, compared with noninjured control specimens (p=.03).

CONCLUSIONS
Immunoreactive TNF is present in normal pig coronary arteries, and there is an induction of TNF mRNA early after balloon angioplasty.

REPORT DATE: 10/15/92 WORK UNIT # 1265

DETAIL SUMMARY SHEET

TITLE: Cardiac Safety of Sexual Intercourse Following Myocardial Infarction as Assessed by High Resolution Holter Monitor

KEYWORDS: sexual intercourse, myocardial infarction, Holter monitor

PRINCIPAL INVESTIGATOR: Prewitt, Kerry CPT MC
ASSOCIATES: Cambier, Patrick MAJ MC; Wortham, Dale COL MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the cardiac safety of sexual intercourse following myocardial infarction by directly assessing for the presence of ischemia and dysrhythmias using high resolution Holter monitoring.

TECHNICAL APPROACH

Patients who are 1 month post myocardial infarction will undergo a history, physical examination, and exercise. Patients will then wear a Holter monitor for 24 hours during which time they will have sexual intercourse. Holter studies willbe analyzed for ST segment depression, dysrhythmias, and symptoms.

PRIOR AND CURRENT PROGRESS

A total of 22 patients (7 in the past year) have been enrolled in the study. Enrollment has been limited by a PCS move of an associate investigator and a 6 month TDY by the principal investigator. There have been no adverse reactions. There has been no direct patient benefit.

CONCLUSIONS

No conclusions can be made until all the data is collected.

REPORT DATE: 06/08/93 WORK UNIT # 1267

DETAIL SUMMARY SHEET

TITLE: Cholesterol and Recurrent Events

KEYWORDS: cholesterol, pravastatine, therapy

PRINCIPAL INVESTIGATOR: Gorman, Patrick MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: May 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether intensive therapy to lower plasma cholesterol will decrease fatal and nonfatal coronary heart disease and/or cause mortality in patients who have had infarction and do not have "high risk" cholesterol.

TECHNICAL APPROACH
Patients with r/o MI who do not have high risk cholesterol will be randomized to placebo or pravastatine. At least 8 weeks after infarction, patients will be screened by EKG, lab, and MUGA as indicated. Those enrolled will begin "run-in" placebo therapy. Thereafter, the patient will complete randomization with Hx/PE, dietary counseling, lipid profile, and safety lab every 3 months for the 5-year study, and yearly eye exams, and EKG's.

PRIOR AND CURRENT PROGRESS
Recruitment of subjects for this study was completed in November 1991, with four patients enrolled. There will be no further patient enrollment There have been no incidents of serious or unexpected adverse reactions. Data collection and processing is in progress by the main study site in Houston, TX.

CONCLUSIONS
Data collection and analysis is in progress.

REPORT DATE: 07/13/93 WORK UNIT # 1268

DETAIL SUMMARY SHEET

TITLE: Intracoronary Pacing: Acute and Longterm Safety, Efficacy During Ischemia, and Efficacy in Epicardial Pace-Mapping

KEYWORDS: pacing, coronary, ischemia

PRINCIPAL INVESTIGATOR: Stajduhar, Karl MAJ MC
ASSOCIATES: Hull, Robert MAJ MC; Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 1,864 Previous FYs: $ 2,236 Total: $ 4,100

STUDY OBJECTIVE

To determine extent of acute histologic damage in coronary arteries produced by intracoronary pacing; to determine the spectral resolution of intracoronary pace mapping; and to examine intracoronary pacing thresholds during severe myocardial ischemia.

TECHNICAL APPROACH

For the first objective, an intracoronary pacing electrode will be positioned in different locations and intracoronary cardiac pacing performed. Animals will recover for 1 day, then be euthanized. The coronary arteries will be examined histologically for extent of damage. For the second objective, the intracoronary electrode will be withdrawn during pacing to identify significant surface EKG changes to determine the spectral resolution of this technique. Finally, during coronary pacing, ischemia will be produced by PTCA balloon inflation, and pacing thresholds will be serially assessed.

PRIOR AND CURRENT PROGRESS

All phases of this protocol have been completed. The histologic and pacemapping resolution portions are currently under analysis. The portion dealing with pacing thresholds during acute ischemia has been accepted for publication and will be published in Cardiovascular Catheterization and Diagnosis.

CONCLUSIONS

The final two phases of this protocol still require review of histology by the AFIP, data analysis, and manuscript preparation.

REPORT DATE: 07/16/93 WORK UNIT # 1269

DETAIL SUMMARY SHEET

TITLE: The Porcine Restenosis Model: Characterization of the Vascular Proliferative Response to Injury

KEYWORDS: coronary vascular injury, intracoronary stents, smooth muscle cell

PRINCIPAL INVESTIGATOR: Carter, Andrew MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 4,310 Previous FYs: $ 5,091 Total: $ 9,401

STUDY OBJECTIVE
To induce consistent smooth muscle cell proliferation after coronary vascular injury using metallic stents.

TECHNICAL APPROACH
The study involves placement of metallic intracoronary stents via aseptic carotid cutdown in the porcine model.

PRIOR AND CURRENT PROGRESS
Altogether, 38 stents were implanted in 30 animals; 5 animals were used this past year. The time course of lesion morphology, neointimal cell proliferation and characterization was studied with vessel morphometry, quantitative angiography, and immunohistochemistry. Neointimal cell proliferation was measured with proliferating cell nuclear antigen. The percent of cells positive for proliferating cell nuclear antigen per high power field was recorded at serial time points after stent placement. Intimal cell type was further characterized with alpha-actin and Movat pentachrome.

CONCLUSIONS
Intimal cell proliferation is greatest at 7 days after stenting, with minimal proliferation by 28 days. Neointimal matrix synthesis follows smooth muscle cell proliferation, and the rate of matrix expansion was greatest between 7 and 14 days.

REPORT DATE: 07/16/93 WORK UNIT # 1270

DETAIL SUMMARY SHEET

TITLE: Electrophysiologic Identification of Concealed Accessory Pathway Conduction as a Potential Predisposing Factor in "Lone" Atrial Fibrillation

KEYWORDS: fibrillation, electrocatheters, predisposing factor

PRINCIPAL INVESTIGATOR: Wiley, Thomas MAJ MC
ASSOCIATES: Hull, Robert MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the electrophysiologic substrate in patients with lone atrial fibrillation compared with control patients undergoing electrophysiologic studies for syncope.

TECHNICAL APPROACH

The patients are taken to the Cardiac Catheterization Laboratory in the post-absorptive and sedated state. Multipolar electrocatheters are then placed in the high right atrium, bundle region, right ventricular apex, and coronary sinus. Programmed burst and progressive decremental pacing is then performed from the right ventricular apex and the high right atrium.

PRIOR AND CURRENT PROGRESS

There have been 3 patients and 2 controls enrolled in the last year, for a total of 13 patients and 4 controls. No unexpected or serious adverse outcomes or reactions have resulted from patient participation. Two patients were diagnosed with reentrant tachycardias, and as a result, their therapies were significantly altered.

CONCLUSIONS

This project is going better than expected. If evidence of dual AV node physiology continues at the present rate, statistical significance will be attained much earlier than anticipated.

REPORT DATE: 10/28/92 WORK UNIT # 1272

DETAIL SUMMARY SHEET

TITLE: Pharmacokinetic Drug Interactions with Terfenadine

KEYWORDS: terfenadine, pharmacokinetics, cardiac repolarization

PRINCIPAL INVESTIGATOR: Cantilena, Louis MD PhD
ASSOCIATES: Wortham, Dale COL MC

DEPARTMENT: Department of Medicine ST: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the biotransformation of terfenadine is altered by several known inhibitors of drug metabolism. To determine if such altered metabolism is found to occur whether there may be associated electrocardiographic changes.

TECHNICAL APPROACH
Volunteer, otherwise healthy, subjects will be given FDA-recommended dose of terfenadine (60 mg BID) for 1 week. Blood will be sampled during dosing interval at end of 1 week. Subjects will then be started on potential inhibitor of interest for second week while continuing terfenadine. Second pharmacokinetic profile will be performed at the end of the second week. Electrocardiograms will be performed at baseline, after 1 week of terfenadine, and daily pre-dose after starting the inhibitors. Subjects wear Holter monitors during blood profiles to allow for concentrations effect analysis. For safety purposes, subjects will be hospitalized on telemetry for first 72 hours of inhibitor.

PRIOR AND CURRENT PROGRESS
To date, studies have been completed investigating the interaction of terfenadine with cimetidine, ranitidine, erythromycin, clarithromycin, azithromycin, fluoconazole, and ketoconazole. Six subjects participated in each cohort, for a total of 42 completed volunteers; the researchers plan to enroll 6 more subjects. Significant pharmacokinetic and ECG effect with ketoconazole and erythromycin has been seen. There have been no serious or unexpected adverse reactions, and no patients withdrew from the study. There has been no direct benefit to any volunteer. An addendum has been submitted to investigate the effect of itraconzole.

CONCLUSIONS
The FDA and DCI sponsored research has made an important contribution to public health in U.S. Since hearing preliminary data, the FDA has contraindicated the concomitant use of ketoconazole, erythromycin, and terfenadine.

REPORT DATE: 01/12/93 WORK UNIT # 1273

DETAIL SUMMARY SHEET

TITLE: A Study Investigating the Safety and Duration of Effect of Isosorbide-5-Mononitrate in a Controlled-Release Formulation in Patients with Stable Effort Angina Pectoris

KEYWORDS: angina pectoris, nitrates, stress testing

PRINCIPAL INVESTIGATOR: Pearson, Clarence LTC MC
ASSOCIATES: Gurczak, Patricia MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the chronic antianginal efficacy and safety of isosorbide-5-mononitrate in a controlled-release formulation at 12 and 24 hours after administration in patients with chronic stable angina and objective evidence of ischemia. Also, to demonstrate that patients do not develop tolerance to the nitrate preparation.

TECHNICAL APPROACH

This is an 8-9 week, outpatient, multicenter, double-blind, parallel group study where the efficacy of the agent is determined by serial treadmill testing. The study consists of two parts. Part A is a 2-3 week single-blind safety phase, during which the study patients will be randomly assigned to receive either placebo or isosorbide-5-mononitrate in a controlled release formulation. Part B consists of serial treadmill testing, pre and post oral administration of the medicine, and repeat treadmills 12 hours later.

PRIOR AND CURRENT PROGRESS

Twenty-three patients were screened for possible inclusion in the study; six of them were found eligible and were enrolled. All six patients completed Part A; four did not continue to Phase B because they didn't meet eligibility requirements. The two remaining patients completed Phase B (and thus the entire study). There were no serious or unexpected adverse reactions.

CONCLUSIONS

None yet. This is a double-blind, placebo-controlled study, which is not complete at this time.

REPORT DATE: 01/11/93 WORK UNIT # 12[illegible]

DETAIL SUMMARY SHEET

TITLE: Transcoronary Mapping of Accessory Pathways in Patients Undergoing Percutaneous Accessory Pathway Radiofrequency Ablation

KEYWORDS: accessory pathway, radiofrequency ablation, coronary mapping

PRINCIPAL INVESTIGATOR: Hull, Robert MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the safety and efficacy of an intracoronary electrode catheter in the localization of accessory pathways in patients who are to undergo ablative therapy.

TECHNICAL APPROACH
After arrythmia induction, an 8 F arterial sheath will be inserted, and 10,000 U of heparin administered. The over-the-wire catheter will be inserted into the coronary artery through a guiding catheter. The over-the-wire catheter will then be pulled back into the guiding catheter while recording coronary electrograms during ventricular pacing or tachycardia. After localizing the pathway, the catheter will be removed, and the remainder of the patient's procedure will be completed.

PRIOR AND CURRENT PROGRESS
This study involved the acceptance of the coronary electrode mapping catheters as an IDE. Final approval to begin the study was received from HSC in August 1992. Scheduling conflicts since that time have reduced recruitment possibilities; however, this was temporary.

CONCLUSIONS
This is a vital study that can greatly facilitate the study of Wolff-Parkinson-White syndrome.

REPORT DATE: 07/15/93 WORK UNIT # 1275

DETAIL SUMMARY SHEET

TITLE: Percutaneous Balloon Pericardotomy for the Treatment of Pericardial Effusion/Tamponade

KEYWORDS: balloon, pericardial window

PRINCIPAL INVESTIGATOR: Laird, John MAJ MC
ASSOCIATES: Gorman, Patrick MAJ MC; Prewitt, Kerry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study the effectiveness of a new percutaneous technique of balloon pericardiotomy for the treatment of pericardial effusion and cardiac tamponade/impending tamponade. This involves the use of large balloons, similar to the balloons used for balloon valvuloplasty, to create a pericardial window.

TECHNICAL APPROACH

The study is being performed as part of a multicenter registry with the goal of evaluating the therapeutic efficacy and risks of percutaneous balloon pericardiotomy. The study will also evaluate and modify technical aspects of percutaneous balloon pericardiotomy for the treatment of pericardial effusion.

PRIOR AND CURRENT PROGRESS

No patients were enrolled in the study during this time period.

CONCLUSIONS

None.

REPORT DATE: 08/17/93 WORK UNIT # 1276

DETAIL SUMMARY SHEET

TITLE: CAVEAT II. A Study Investigating the Primary and Long-Term Outcome in Patients with De Novo Vein Graft Lesion Randomly Assigned to Either Balloon Angioplasty or Directional Atherectomy

KEYWORDS: baloon angioplasty, direction atherectomy, restenosis

PRINCIPAL INVESTIGATOR: Pearson, Clarence LTC MC
ASSOCIATES: Gorman, Patrick MAJ MC; Laird, John MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the outcome in patients with de novo vein graft lesions assigned to either balloon angioplasty (PTCA) or directional atherectomy (DCA). The hypothesis being tested in whether 6 month restenosis rates are lower in patients with de novo vein graft lesions.

TECHNICAL APPROACH

Patients who meet the angiographic criteria will be identified and will be randomized to receive either PTCA or DCA. The patients will undergo the procedure and return in 6 months for a repeat stress test and cardiac catherization. All interval cardiovascular events (fatal or non-fatal) will be recorded.

PRIOR AND CURRENT PROGRESS

A total of four patients have been enrolled to date. There have been no serious or unexpected adverse reactions, and no patients have withdrawn. Two of the four patients returned for angiographic follow-up, and another will return this month. All patients benefited. Two of four patients show no sign of restenosis, as evidenced through both angiography and clinical diagnosis; one had DCA and the other had PTCA. The other two patients experienced return of their angina; one of them underwent a repeat procedure.

CONCLUSIONS

The numbers are too small to draw major conclusions, other than both of these procedures can be performed safely and effectively.

REPORT DATE: 01/05/93 WORK UNIT # 1815

DETAIL SUMMARY SHEET

TITLE: Investigation of a Viral Etiology in Pityriasis Rosea

KEYWORDS: pityriasis rosea, picornavirus, polymerase chain reaction

PRINCIPAL INVESTIGATOR: James, William COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Dermatology Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 1,100 Total: $ 1,100

STUDY OBJECTIVE
To attempt to amplify viral DNA fragments using picornavirus primers in skin biopsies from patients with pityriasis rosea using the polymerase chain reaction.

TECHNICAL APPROACH
Punch biopsies from the cutaneous rash of patients with pityriasis rosea will be done. Blood will be drawn at the same time, centrifuged and frozen. A single step method of RNA extraction will be done with the acid guanidinum thiocyanate-phenol-chloroform method. The polymerase chain reaction will be done on the specimen after RNA extraction using reverse transcriptase reaction initially and then the amplification process.

PRIOR AND CURRENT PROGRESS
Fourteen patients and five controls have had biopsies taken; no new patients have been enrolled this past year. Currently these skin specimens are undergoing analysis by the methods described. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
No definitive conclusions are available from the incomplete analysis, to date. It is anticipated this protocol will be completed in the next year.

REPORT DATE: 08/09/93 WORK UNIT # 1816

DETAIL SUMMARY SHEET

TITLE: Comparison of Scalp Biopsy and Hair Pluck in the Evaluation of Hair Loss

KEYWORDS: scalp biopsy, hair pluck

PRINCIPAL INVESTIGATOR: Vogel, Paula CPT MC
ASSOCIATES: Sperling, Leonard LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the results obtained from a scalp biopsy and a hair pluck at adjacent sites performed on the same day in patients with hair loss.

TECHNICAL APPROACH
A hair pluck and two scalp biopsies will be performed at adjacent sites to the affected area. A hair pluck and one scalp biopsy will be performed at adjacent sites to a normal area.

PRIOR AND CURRENT PROGRESS
Seventeen patients with hair loss of various etiologies were enrolled and evaluated with biopsy and hair plucks. There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
The mean hair shaft diameters and the percentage telogen hairs were compared. No significant difference between biopsy and pluck diameter was found. No significant difference between affected and unaffected sites was found. A significant difference (p=.007) between biopsy and pluck percent telogen was found.

REPORT DATE: 08/03/93 WORK UNIT # 1302-88

DETAIL SUMMARY SHEET

TITLE: Cholestyramine Treatment of Thyrotoxicosis

KEYWORDS: cholestyramine, thyroid, thyrotoxicosis

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Solomon, Barbara DNSc; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Mar 1988

FUNDING: Current FY: $ 9,875 Previous FYs: $ 15,376 Total: $ 25,251

STUDY OBJECTIVE

To investigate the use of oral cholestyramine as a safe and rapid method of lowering serum thyroxine levels in hyperthyroid patients.

TECHNICAL APPROACH

A randomized, placebo crossover controlled design will be used. Subjects will receive 4 grams cholestyramine powder four times a day or an equal amount of placebo powder for 14 days, no powders for 7 days, and then the reciprocal powder for 14 days. Serum T4 and T3 will be measured throughout each period.

PRIOR AND CURRENT PROGRESS

Fifteen subjects have been enrolled (none during the past year); seven received cholestyramine, and eight received placebo during Phase 1. A more rapid decline in all thyroid hormone levels was seen in the cholestyramine-treated group ($F=4-7$, $p<0.01$) than in the placebo group ($F=2-3$, $p<0.05$). All patients then proceeded to Phase 2. In Phase 2, the eight patients who received cholestyramine showed an additional decline in free thyroxine from weeks 1 to 2, but the overall rate of decline in hormone levels was not different between the groups. Immunoglobulin levels remained unaffected regardless of group, treatment, or time. A total of 15 patients participated in the study, with no adverse effects.

CONCLUSIONS

Cholestyramine is a safe and effective adjunctive agent in the treatment of thyrotoxicosis, and its greatest efficacy may be during the first few weeks of treatment.

REPORT DATE: 09/10/93 WORK UNIT # 1303-88

DETAIL SUMMARY SHEET

TITLE: The Clinical Application of In Situ Hybridization to Detect Viral Genomes and Oncogenes in Diseases of the Thyroid and Selected Viral Infections

KEYWORDS: virus, thyroid, probes

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Humphrey, Michael MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Apr 1988

FUNDING: Current FY: $13,311 Previous FYs: $ 0 Total: $ 13,311

STUDY OBJECTIVE
To determine if viral elements are important in thyroid disease.

TECHNICAL APPROACH
Both Southern and Northern blots and in situ hybridization studies will be used to determine if viruses are present in thyroid tissue from patients with various thyroid disorders. Polymerase chain reaction (PCR) and cloning techniques willalso be employed.

PRIOR AND CURRENT PROGRESS
Twenty-five patients have been enrolled in this study (5 this past year). There has been no incidence of serious or unexpected adverse reactions. The study has shown that HIV-like viruses are absent in thyroid glands and white cells of patients with autoimmune thyroid disease (Lancet 1991;337:17). Since that time, work has been directed toward developing techniques to assess the presence of other viruses or virus-like material, such as oncogenes. Attempts have been made to develop a reliable system of measuring p53 (an oncogenic virus) in samples, but they have not been successful.

CONCLUSIONS
A viral agent essential to autoimmune thyroid disease has not yet been identified.

REPORT DATE: 12/03/92 WORK UNIT # 1311-88

DETAIL SUMMARY SHEET

TITLE: Incidence of Fractures in Post-Menopausal Women

KEYWORDS: fractures, thyroid hormone, postmenopausal

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc
ASSOCIATES: Wartofsky, Leonard COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 300 Previous FYs: $ 658 Total: $ 958

STUDY OBJECTIVE

To determine whether having thyroid disease or taking thyroid hormone is a risk factor for fractures in postmenopausal women.

TECHNICAL APPROACH

Data will be collected via survey.

PRIOR AND CURRENT PROGRESS

Data collection began in September 1989 at Nolwood Retirement Community. One hundred fifty-three of the 270 residents consented to be interviewed. Additional subjects were recruited from the patient population of the Thyroid Clinic, WRAMC. Data collection was suspended in December 1990 due to the temporary reassignment of the PI during Desert Storm; with a total of 227 subjects entered by this date. Data collection was reinstituted in August 1991, with a total of 300 interviews completed by November 1991. Of the 300 postmenopausal women, 160 had thyroid disease and 140 did not have thyroid disease. No further data collection is anticipated.

CONCLUSIONS

Postmenopausal white women with a history of thyroid disease do not have more hip, vertebral, or forearm fractures than other postmenopausal white women. The dose or duration of thyroid hormone therapy, duration of disease, or use of calcium or estrogen did not influence the type or number of fractures. Women with a history of hyperthyroidism are at risk of having a fracture at a younger age than other women.

REPORT DATE: 04/27/93 WORK UNIT # 1312-89

DETAIL SUMMARY SHEET

TITLE: Treatment of Oligospermia with Antiestrogens

KEYWORDS: oligospermia, clomiphene, tamoxifen

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 737 Total: $ 737

STUDY OBJECTIVE
To compare the effectiveness of tamoxifen and clomiphene in treating oligospermia.

TECHNICAL APPROACH
Randomized, prospective study of clomiphene, 25 mg every other day, and tamoxifen, 10 mg twice daily, for treatment of idiopathic oligospermia.

PRIOR AND CURRENT PROGRESS
Due to personnel shortages, the male infertility clinic was temporarily suspended during the past year. Consequently, no patients were under study on this protocol during the past year. A total of 10 patients have been entered into this study. There has been no incidence of unexpected or serious adverse reactions. It is hoped that it will be possible to reopen the male infertility clinic and resume work on this protocol within the next 6-12 months.

CONCLUSIONS
None.

REPORT DATE: 07/12/93 WORK UNIT # 1316-89

DETAIL SUMMARY SHEET

TITLE: Identification of Unique Nucleotides in the Thyroid Gland of Patients with Various Thyroid Disorders

KEYWORDS: thyroid, gene, RNA

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Nagy, Endre MD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $10,082 Previous FYs: $ 5,006 Total: $ 15,088

STUDY OBJECTIVE
To identify unique thyroid genes that are expressed in autoimmune thyroid disease and cancer.

TECHNICAL APPROACH
Construct cDNA library from thyroid tissue of patients with autoimmune thyroid disease and cancer. The cDNA library is then screened by labelling RNA or cDNA from the tissue of interest.

PRIOR AND CURRENT PROGRESS
Several unique clones have been identified from patients with autoimmune thyroid disease. These clones have been sequenced and divided into three categories: NADH dehydrogenase related, thyroglobulin related, and undescribed. In addition, specific monoclonal antibodies have been used to identify amino acids 890-965 of TG and amino acids 1564-1623 of TB as potentially immunogenic. Peptides 271-394 of the TSH receptor have also been identified as immunogenic. To date, 60 patients have been studied; 40 have been enrolled during the past year. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Areas of immunogenicity of TG and TSHR have been identified.

REPORT DATE: 05/28/93 WORK UNIT # 1322-90

DETAIL SUMMARY SHEET

TITLE: Treatment of Impotence in Diabetic Men

KEYWORDS: impotence, diabetes, yohimbine

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,477 Total: $ 1,477

STUDY OBJECTIVE

To compare the effectiveness, acceptance, and complication rate of an externally applied vacuum device versus yohimbine for the treatment of impotence in the diabetic male population, and to identify any specific characteristics of patients who respond favorably to each therapy.

TECHNICAL APPROACH

Diabetic men presenting to the Endocrine Clinic will be screened to determine the status of erectile function. All subjects with erectile dysfunction will be offered participation. Evaluation will consist of history and physical, routine and endocrine lab testing, and urologic consultation. Testing will be conducted in 3-month phases with yohimbine and Erec-Aid. Initial form of therapy will be randomized with a 3-month washout period between therapeutic periods. The only protocol change involves the urologic examination, which is generally being conducted on an outpatient rather than inpatient basis.

PRIOR AND CURRENT PROGRESS

Twenty-two patients have been entered in this study; none this past year. Ten patients have completed or nearly completed the protocol. No adverse effects have occurred as a result of either modality. Use of the Erec-Aid proved effective and was well tolerated in the majority of patients, while yohimbine resulted in little improvement. Dr. Humphrey has been reassigned to Ft. Bragg, and recruitment has stopped.

CONCLUSIONS

None. Protocol should be closed.

REPORT DATE: 05/17/93 WORK UNIT # 1324-90

DETAIL SUMMARY SHEET

TITLE: Use of Corticotropin Release Hormone in the Evaluation of Hypercortisolemia and Hypocortisolemia

KEYWORDS: hypercortisolemia, hypocortisolemia, Cushing's syndrome

PRINCIPAL INVESTIGATOR: Schaaf, Marcus MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To define the source of excessive adrenocarticotropic hormone (ACTH) production in ACTH-dependent Cushing's syndrome (pituitary or ectopic), and to help in differentiating other temporary hypercortisolemic states, such as depression. Additionally, hypocortisolemic patients with low ACTH values will be examined to distinguish hypothalamic versus pituitary cause.

TECHNICAL APPROACH

Corticotropin-releasing hormone (CRH) 1.0 ug/kg will be administered over 1 to 2 minutes into a peripheral vein with peripheral venous blood sampling for ACTH and cortisol at -15, -1, +5, +15, +30, and +60 minutes. When CRH is administered during inferior petrosal sinus (IPS) sampling for localization of pituitary ACTH-secreting tumors, blood from both right and left sinuses and a peripheral vein will be sampled at 3, 5, and 10 minutes after CRH.

PRIOR AND CURRENT PROGRESS

No CRH tests were performed during the past year, and thus no new subjects were enrolled. To date, only two patients have entered this study due to the fact that patients meeting eligibility criteria are rare, as well as radiologic support (now improved) has been inadequate. One patient with Cushing's syndrome presented for evaluation during the past year. Standard tests suggested a pituitary source of excess ACTH with negative pituitary imaging. Since inferior petrosal sampling (IPS) was not available through Radiology, the patient was referred to the NIH for sampling with CRH testing. A patient with occult ectopic ACTH, as defined by previous peripheral and IPS/CRH testing, continues to be followed. The patient is currently controlled without a defined source of ACTH. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

CRH testing during IPS sampling remains the most discriminating means of identifying the hypercortisolemic patient with excess ACTH of pituitary origin (requiring pituitary surgery) from the patient with ectopic ACTH production (requiring localization and removal of the ACTH-producing tumor) for potential cure. FDA approval of CRH is still pending.

REPORT DATE: 10/26/92 WORK UNIT # 1328-90

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Thyrotropin Releasing Hormone Regulation of Thyrotropin Gene Expression

KEYWORDS: TRH, TSH, gene

PRINCIPAL INVESTIGATOR: Carr, Frances PhD
ASSOCIATES: Smallridge, Robert COL MC; Fisher, Carolyn BS

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $39,754 Previous FYs: $ 45,637 Total: $ 85,391

STUDY OBJECTIVE

To determine: 1) the DNA sequence(s) essential for mediating TRH stimulation of TSH gene expression, 2) the role of calcium and protein kinase C as intracellular signaling events, and 3) the potential involvement of proto-oncogenes (JUN, FOS) in this system.

TECHNICAL APPROACH

Deletion/mutation analysis of TSHB subunit gene in reporter plasmid vectors monitored in transient expression assays (cell culture). Stimulation and inhibition of intracellular pathways and monitoring these effects on TRHB gene promoter activity. Measurement of JUN/FOS mRNA levels in transiently transfected cells in response to TRH in the presence/absence of intracellular stimulators inhibitors. Determine the effect of antisense RNA's to JUN/FOS on TRH actions. Determine DNA:protein interactions by gel shift, Southwestern hybridizations.

PRIOR AND CURRENT PROGRESS

Previous work determined that TRH stimulated TSHB gene promoter activity in transiently transfected pituitary GH3 cells is similar to in vivo conditions. The DNA sequences required to mediate TRH action have now been localized to -231 to -261. A second minor response region is contained within -211 to -251. The prominent region also mediates stimulation by calcium mobilization and protein kinase C, confirming a convergence of these pathways in gene regulation. The DNA binding proteins are duplicated in multiple regions, but specific proteins are also detected for each region.

CONCLUSIONS

TRH stimulation of TSHB gene expression is mediated in part by calcium mobilization and protein kinase C activation. TRH stimulation of JUN and FOS may be key in stimulation of TSH synthesis. Two regions mediate TRH action, but only one region mediates convergence of the intracellular signalling pathways with TRH.

REPORT DATE: 12/15/92 *WORK UNIT # 1329-90

DETAIL SUMMARY SHEET

TITLE: Search for p53 Genetic Abnormalities in Tissue obtained from Normal and Pathological Thyroid Glands

KEYWORDS: p53, thyroid, carcinoma

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 236 Total: $ 236

STUDY OBJECTIVE
To investigate the nature of qualitative and quantitative p53 alterations in pathological thyroid tissue.

TECHNICAL APPROACH
The use of immunohistochemical staining of tissue obtained at the time of surgery. Specimens will include thyroid tissue and non-thyroid (controls) tissue. The addition of controls was approved in an addendum to the HUC/IRB in January 1992. Commercially acquired antibodies which recognize both wild-type and mutant human p53 will be utilized. Gene sequencing is carried out via polymerase chain reaction (PCR) amplification of sequences, followed by DNA sequencing.

PRIOR AND CURRENT PROGRESS
Initial attempts to stain tissues were largely unsuccessful. However, PCR has been used to analyze p53 abnormalities in conjunction with SSCR. These studies will begin (after needed preliminary studies are performed) and will extend to related oncogenes and viruses.

CONCLUSIONS
None yet.

REPORT DATE: 04/15/93 WORK UNIT # 1330-90

DETAIL SUMMARY SHEET

TITLE: A 16 Week Double-Blind Placebo Controlled Dose Response Study Using Glipizide GITS Tablets for the Treatment of Noninsulin Dependent Diabetes Mellitus

KEYWORDS: diabetes mellitus, glipizide GITS, treatment

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 2,888 Previous FYs: $ 0 Total: $ 2,888

STUDY OBJECTIVE
To evaluate the efficacy and safety of glipizide GITS in the treatment of patients with non-insulin-dependent diabetes mellitus (NIDDM); to define the dose response relationship with glipizide GITS; and to assess the long-term safety and efficacy of glipizide GITS.

TECHNICAL APPROACH
Patients with NIDDM will be enrolled and in a double-blind fashion will be given one of the following doses of glipizide GITS: placebo, 5 mg, 20 mg, or 60 mg per day. Weekly measurements of plasma glucose and intermittent measurements of hemoglobin A1C, insulin, and drug levels will be performed over a period of 16 weeks. After this, the patients will be enrolled in the open-label, long-term treatment phase of the study.

PRIOR AND CURRENT PROGRESS
During the first year, 14 patients were enrolled in the first phase of the study. All but one patient, who moved from the area, continued in the open-label trial (13). Since the last report, two patients have been dropped from the study due to poor diabetes control and have been changed to insulin. The remaining 11 patients are approaching or have been seen for their 18 month visit and are doing well. There have been no observed adverse effects from the study medication. Participants will be continued on the study drug for evaluation of long-term safety in conjunction with Pfizer, Inc. This center is one of 10 sites participating in the study. Pfizer, Inc. is analyzing the data of all sites for possible publication.

CONCLUSIONS
Glipizide GITS seems safe and efficacious in the treatment of NIDDM.

REPORT DATE: 02/19/93 WORK UNIT # 1331-91

DETAIL SUMMARY SHEET

TITLE: Response of Multinodular Goiters with Substernal Extension to Therapeutic Doses of Iodine-131

KEYWORDS: multinodular goiter, substernal goiter, iodine 131

PRINCIPAL INVESTIGATOR: Mahoney, Karen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 3,221 Total: $ 3,221

STUDY OBJECTIVE
To determine the effect of moderate doses of radioactive iodine on reduction of size and control of symptoms in patients with large multinodular goiters.

TECHNICAL APPROACH
After informed consent, patients will be admitted to the Kyle Metabolic Unit. They will undergo an iodine 131 scan and uptake, as well as computerized tomography (CT) scanning and chemical thyroid function testing. Iodine 131 is administered in an approximate dose to deliver 100-150 uCi/gm of tissue. After observation for 5 to 10 days, patients will be discharged and followed up as outpatients. Outpatient follow-up will include thyroid function testing and CT at 6, 12, and 24 months to determine response to treatment.

PRIOR AND CURRENT PROGRESS
Four new subjects were enrolled in the past year, bringing the total to 10. In the previous study period, one patient developed an elevated hemidiaphragm; it is not clear if this was study-related. Otherwise, there have been no significant adverse reactions. The average percent goiter volume decline at 6 months has been 26% (range 11-33%); at 12 months it has been 53% (43-61%), and at 18 months it has been 60% (57-63%). All patients have had a decline in their volume. The nunmber of patients is probably too small to make firm conclusions yet, but it appears that the therapy is resulting in a goiter volume decrease in all patients and that the decline in volume continues to be significant beyond 6 months after therapy. This therapy appears to have benefitted all enrolled in terms of goiter volume decrease.

CONCLUSIONS
The decline in goiter volume in all enrolled patients appears significant, and if this trend persists in future subjects, Iodine 131 therapy for multinodular goiter may present a viable alternative to surgical therapy.

REPORT DATE: 03/04/93 WORK UNIT # 1332-91

DETAIL SUMMARY SHEET

TITLE: Thermogenic Agent Promotion of Weight Loss in Obese Soldiers

KEYWORDS: thermogenic, promotion, obese

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test whether thermogenic agents will enhance weight loss while subjects are on a low and maintenance caloric diet.

TECHNICAL APPROACH
Two groups repeated measures design. Groups are either placebo or agent, with further division between men and women.

PRIOR AND CURRENT PROGRESS
No patients have been entered into this study due to persistent difficulties obtaining a placebo from outside sources and the inability of the WRAMC pharmacy to make a placebo tablet.

CONCLUSIONS
No further attempts will be made to implement this study.

REPORT DATE: 04/30/93 WORK UNIT # 1333-91

DETAIL SUMMARY SHEET

TITLE: Endothelin and Cultured Human Thyroid Cells

KEYWORDS: endothelin, thyroid, human

PRINCIPAL INVESTIGATOR: Jackson, Sharon MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $13,369 Previous FYs: $ 17,635 Total: $ 31,004

STUDY OBJECTIVE

To determine the interaction of endothelin and cultured human thyroid cells (CHTC) with regard to: the characteristics of endothelin binding and the endothelin receptor, the effect of endothelin binding on CHTC and the mechanism involved, and the interaction of endothelin and other growth factors in CHTC. Also, to determine the significance of abnormal serum endothelin levels in patients with thyroid disease.

TECHNICAL APPROACH

Thyroid tissues obtained at surgery are digested with collagenase, and the isolated follicular cells are cultured. Competitive binding studies are performed using radiolabelled endothelin, and modulation of binding by other growth factors is assessed. Levels of endothelin and other hormones are measured in the culture media, and changes in thymidine incorporation are determined. Serum levels of endothelin in patients with thyroid disorders are also measured by radioimmunoassay.

PRIOR AND CURRENT PROGRESS

Since the last report, 12 patients have given consent to donate thyroid tissue obtained at surgery; 26 altogether. Ten subjects have had blood samples drawn for endothelin levels while on the Kyle Metabolic Unit; 55 altogether. No patient has had a serious or unexpected adverse reaction, and none have been withdrawn from the study. The total number of subjects enrolled to date is 81.

CONCLUSIONS

A previously unknown interaction of endothelin in the thyroid has been demonstrated, which is likely to be only a part of a complex interaction of growth factors. The specifics of these interactions and the significance of endothelin in thyroid diseases remain to be determined.

REPORT DATE: 05/17/93 WORK UNIT # 1334-91

DETAIL SUMMARY SHEET

TITLE: A Search for Glycosylated Insulin in Patients with Non-Insulin Dependent Diabetes Mellitus

KEYWORDS: diabetes, insulin, glycosylated

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1991

FUNDING: Current FY: $47,682 Previous FYs: $ 1,043 Total: $ 48,725

STUDY OBJECTIVE

To determine if patients with non-insulin dependent diabetes mellitus (NIDDM) produce from the beta cells of their pancreas an abnormal insulin variant which is glycosylated prior to release from the beta cell. This posttranslational modification may hinder binding and activation of the insulin receptor in target tissues.

TECHNICAL APPROACH

Insulin will be extracted from 30cc of the patient's blood via affinity chromatography using a polycolonal insulin antibody. The eluated insulin will be further purified with the use of a Sep Pac cartridge and then subjected to polyacrylamide gel electrophoresis using high density gels. After electrophoresis, the gels will be stained with silver stain or immunostained for carbohydrate or insulin using various antibodies. The above will be done before or after deglycoslyation with N-glycosidase.

PRIOR AND CURRENT PROGRESS

To date, blood has been drawn on 60 patients (10 during the past year), and 4 controls (none during the past year). The presence of carbohydrate in the 8300 NW protein of three patients has been confirmed and is believed to be insulin. However, the identity of this protein by immunostaining has not been confirmed due to its small size, small amount, and possibly due to chemical alteration of the protein during the purification process. Currently, a new electrophoretic method is being tried that uses specially-treated Whatman immunoblot paper to achieve a better transfer of the protein so that it can be characterized by immunostaining methods. Once the abnormal protein has been identified the testing of the sera from the other patients, which remains in frozen storage, will be restarted.

CONCLUSIONS

The presence of an abnormal circulating insulin in a subgroup of NIDDM patients may have been identified. Further improvements in purification and identification techniques should elucidate the chemical and immunological identity of this peptide.

REPORT DATE: 06/22/93 WORK UNIT # 1335-91

DETAIL SUMMARY SHEET

TITLE: The Preparation of a Selective Pericentromeric Chromosome 10 YAC (Yeast Artificial Chromosome) DNA Library to Further Define MEN2 Gene Location

KEYWORDS: YAC, MEN II, chromosome 10

PRINCIPAL INVESTIGATOR: Francis, Thomas CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 6,701 Previous FYs: $ 28,343 Total: $ 35,044

STUDY OBJECTIVE
To develop yeast artificial chromosome cloning techniques; to construct a chromosome 10 specific yeast artificial chromosome library; to identify MEN II marker clones and construct a contiguity; and, to use contiguous YAC clones to study MEN II patient DNA for specific location and characterization of gene defects.

TECHNICAL APPROACH
Genomic DNA will be prepared from a human-hamster hybrid cell line, restriction cut to molecular weight >400,000 base pairs, ligated to yeast artificial chromosome vector pYAC4, and then transformed into yeast. Human chromosome 10 clones will be selected and gridded into a permanent library. The library will be screened with known zero and low recombination markers to identify MEN II contiguous clones. These clones will be characterized and used to screen MEN II patient DNA for the defect gene.

PRIOR AND CURRENT PROGRESS
There have been no human blood draws for this study. All work has been performed using existing cell lines. YAC closing skills have been acquired, and major improvements to this evolving technology have been made. "Paste" loading of agar DNA plugs into preparative gels has been developed, which is more rapid and efficient than current methods. The "paste" technique was used to insert a high molecular weight DNA alkaline phosphatase step and show titration which effectively eliminates this mechanism as a cause of chimeric YAC's. "In-gel" ligation to create YAC DNA without melting of the protective agar matrix previously needed to mix vector and insert DNA has been demonstrated. High quality YAC's are now being made, and screening for human chromosome 10 clones, at a very high efficiency compared to most YAC labs with much larger resources, is being initiated.

CONCLUSIONS
This work represents significant improvement in currently published YAC cloning techniques which are at the foundation of the human genome project. The researchers are now efficiently creating a chromosome 10 specific library from hybrid DNA which will dramatically decrease chimerism. However, the major importance of the work is an overall improvement in YAC technology.

REPORT DATE: 10/08/92 WORK UNIT # 1336-91

DETAIL SUMMARY SHEET

TITLE: Investigation of Cross-Reactivity in the Immune Response Against the Human Thyrotropin Receptor and the HIV-1 New Protein in Rabbits

KEYWORDS: thyrotropin, Nef, protein

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $10,419 Previous FYs: $ 6,758 Total: $ 17,177

STUDY OBJECTIVE
To investigate the relevance of an observed amino acid and nucleotide homology between HIV-1 Nef protein and the human TSH receptor (hTSH-R).

TECHNICAL APPROACH
Protein synthesis will be performed using expression PCR. Svnthetic peptide analysis will be done using ELISA and T-cell epitope mapping techniques. Rabbit immunization will be performed with homologous hTSH-R and Nef peptides.

PRIOR AND CURRENT PROGRESS
Rabbit immune response against hTSH-R is cross-reactive against homologous HIV-1 Nef. Rabbit immunization with HIV-1 Nef peptide has been accomplished; immune response is being studied. T-cell response is concurrent to both Nef and hTSH-R peptides in some patients with Graves' disease.

CONCLUSIONS
Immune cross-reactivity between the hTSH-R and HIV-1 suggests that the observed amino acid homology may be sufficient for a shared immune response through molecular mimicry.

REPORT DATE: 10/01/92 WORK UNIT # 1337-91

DETAIL SUMMARY SHEET

TITLE: Treatment of Graves' Disease with Cholestyramine

KEYWORDS: Graves' disease, cholestyramine

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 264 Total: $ 264

STUDY OBJECTIVE
To determine whether adjunctive use of cholestyramine with anti-thyroid drugs in Graves' disease is better than anti-thyroid drugs alone.

TECHNICAL APPROACH
A two-group repeated measured design with random assignment between groups will be used. Group 1 receives Atenolol 50 mg PO qd and Tapazole 30 mg PO qd as standard medical therapy for Graves' disease. Group 2 receives the same medications plus cholestyramine 4 gms four times per day. Subjects are seen weekly for 4 weeks to determine symptom assessment and to obtain blood samples for hormone levels. The principal investigator is blinded to group placement to avoid bias in assessment.

PRIOR AND CURRENT PROGRESS
Seven of the required 24 patients from WRAMC have completed the study. One of the required 24 patients from FAMC has completed the study. There have been no adverse effects from either the standard medical therapy or the adjunctive therapy.

CONCLUSIONS
None.

REPORT DATE: 11/16/92 WORK UNIT # 1338-91

DETAIL SUMMARY SHEET

TITLE: A Sixteen-Week, Open-Label, Two-Way Cross-Over Switch Study Comparing Glucotrol and Glipizide GITS in the Treatment of Non-Insulin Dependent Diabetes Mellitus and An Open-Label, Long-Tern Evaluation of Glipizide GITS for the Treatment of NIDDM

KEYWORDS: diabetes, psychological import, glipizide

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To measure the efficacy of a long-acting form of glipizide, glipizide GITS, in the treatment of diabetes. A secondary objective is to measure the impact of participating in an intensive protocol on patients' self-care activities and their attitudes regarding diabetes care.

TECHNICAL APPROACH
This will be a 16 week open-label, cross-over design and open-label, long-term efficacy trial with an every 3 month follow-up. There are no changes in the original protocol or the addendum. Patients randomized to the control group will not participate in the trial. Hemoglobin A1C and data from questionnaires from this group will be compared to the study group.

PRIOR AND CURRENT PROGRESS
All 18 patients were entered by February 1992; 16 completed the 16-week trial. One died secondary to a cerebral infarction and suspected myocardial infarction at WRAMC; autopsy refused. One patient withdrew due to symptomatic hypoglycemia. Thirteen of the remaining 16 patients continued in the long-term efficacy phase and completed the 3-month follow-up. Three patients were discontinued due to: newly-diagnosed prostate cancer (1), newly-diagnosed endometrial cancer, and unacceptable hyperglycemia (1). After the 16-week trial, the HGA1C level decreased by .8% in the entire study group compared to a 1% increase in the control group ($p < .02$ by ANOVA). The study group also had a significant increase in glucose monitoring activity and exercise and a decrease in "binging" activity, compared to the control group ($p < .05$). Study patients also had improved self-esteem and satisfaction scores compared to no change in the control group.

CONCLUSIONS
Participation in an intensive intervention study for NIDDM patients improves their self-care activities and may contribute to improved glycemic control.

REPORT DATE: 12/24/92 WORK UNIT # 1339-91

DETAIL SUMMARY SHEET

TITLE: Screening a Self-Selected Adult Patient Population for Diabetes Mellitus

KEYWORDS: screening, diabetes

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Linville, Nicky RN; Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 837 Total: $ 837

STUDY OBJECTIVE

To determine whether assessing risk factors for diabetes mellitus and screening for this disease only when one or more risk factors are present (as recommended by the American Diabetes Association) results in an increased proportion of subjects with abnormal screening glucose concentrations.

TECHNICAL APPROACH

This is a retrospective chart review. The risk factors recorded on a written questionnaire by subjects screened by the WRAMC Diabetes Clinic screening program will be reviewed.

PRIOR AND CURRENT PROGRESS

To date, 575 questionnaires have been analyzed. A manuscript has been submitted for publication and is currently being revised.

CONCLUSIONS

The use of a risk factors questionnaire does not increase the percentage of abnormal screening glucose concentrations and, in fact, excludes a significant number of individuals with no risk factors but with abnormal screening glucose concentrations.

REPORT DATE: 12/24/92 WORK UNIT # 1340-91

DETAIL SUMMARY SHEET

TITLE: The Bone Mineral Density of Women Treated with Thyroid Hormone

KEYWORDS: bone, thyroxine, density

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Solomon, Barbara DNSc; Chang, Audrey PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 778 Previous FYs: $ 0 Total: $ 778

STUDY OBJECTIVE
To determine the factors influencing the bone mineral density in women taking thyroid hormone.

TECHNICAL APPROACH
The medical records of women who are taking thyroid hormone and who are having one or more measurements of their bone mineral density will be reviewed.

PRIOR AND CURRENT PROGRESS
To date, 253 medical records have been reviewed. One hundred and ninety-four women have been included in a cross-sectional analysis group and 64 in a longitudinal study group (those who had more than one density measurement).

CONCLUSIONS
No factors related to thyroid hormone administration affect the bone mineral density of the spine. Factors affecting the density of the hip and forearm are currently being analyzed.

REPORT DATE: 04/26/93 WORK UNIT # 1341-92

DETAIL SUMMARY SHEET

TITLE: Recognition of Hospital Malnutrition by Primary Physicians

KEYWORDS: mulnutrition, recognition, primary

PRINCIPAL INVESTIGATOR: Kushner, Jonathan MAJ MC
ASSOCIATES: Martin, Brian LTC MS; Smith, Sandra RD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To perform a cross-sectional and observational study to quantify physicians' awareness of the nutritional state of their inpatients; to document the degree of nutritional assessment and therapeutics undertaken during typical hospitalizations in a major teaching center; and to compare the nutritional assessment of primary care physicians with the assessment of a nutrition support team.

TECHNICAL APPROACH

Chart review of 100 randomly selected adult inpatients evenly distributed throughout the hospital. The chart review will focus on appearance and use of nutrition-related terms; listing of "nutrition" as a problem in notes or problem lists; available objective data such as weight, weight changes, and labs; and nutrition consultations and interventions. Independent assessment of the same 100 patients for nutritional status will be made by interview and exam.

PRIOR AND CURRENT PROGRESS

A total of 100 patients have been enrolled as of March 1992, with chart reviews and interviews completed. Data was tabulated and analyzed July to August 1992, and an abstract was submitted in August 1992. There have been no adverse patient reactions. Benefit: several instances of malnutrition were determined by the study team. These cases were pointed out to the patients in question and to their primary physicians during the study.

CONCLUSIONS

Twenty-six percent of patients in this study appeared to have a degree of malnutrition. Admission weight, weight change history, follow-up weights, and dietary intake documentation were missing in 28-75% of all charts. Nineteen percent of those with mild malnutrition have no nutrition notations in their charts. Inpatient malnutrition is common, and a sizable fraction of all patients do not receive basic screening assessments.

REPORT DATE: 02/22/93 WORK UNIT # 1342-92

DETAIL SUMMARY SHEET

TITLE: The Interaction of Steroids and Atrial Natriuretic Peptide in Cultured Thyroid Cells

KEYWORDS: ANP, glucocorticoids, hydrocortisone

PRINCIPAL INVESTIGATOR: Loughney, Melissa MD
ASSOCIATES: Tseng, Yueh-Chu PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 7,118 Previous FYs: $ 1,304 Total: $ 8,422

STUDY OBJECTIVE

To determine the effects of steroid hormones on atrial natriuretic peptide (ANP) in thyroid cells, and to measure the physiologic response of thyroid cells co-cultured with steroids.

TECHNICAL APPROACH

Surgically obtained human thyroid tissue will be digested with collagenase and then cultured in 24-well plates at a concentration of 100,000 cells per well. Competitive binding studies will be performed using varying concentrations of glucocorticoids and I-125 labelled ANP. The effects of glucocorticoids on the cell media will be analyzed for thyroglobulin (Tg) using ELISA methodology and on the cell growth by thymidine incorporation.

PRIOR AND CURRENT PROGRESS

More than 10 patients have signed consent forms but only 6 thyroid tissues have been received from Pathology. The pathologist used the majority of each thyroid specimen and then provided this study with the remaining tissue not needed for diagnosis. There were no adverse effects in patients, and no direct benefit from the study. The cells that were received were cultured, and various steroids were added to determine their effects.

CONCLUSIONS

Hydrocortisone (HC) at physiologic concentrations stimulated ANP binding in all thyroid tissues studied. HC incubation with thyroid cells for 6 days stimulated secretion. However, this was not mediated through the cAMP pathway. 3-H thymidine incorporation into DNA by thyroid cells was slightly inhibited by HC after 3 days, but this effect was abolished after 6 days.

REPORT DATE: 03/30/93 WORK UNIT # 1343-92

DETAIL SUMMARY SHEET

TITLE: Hormonal Regulation of the Vitamin D Receptor in Human Breast Cancer Cells: A Novel Strategy for Augmenting the Antiproliferative Effectr of Calcitriol

KEYWORDS: vitamin D receptor, breast cancer, antiproliferative

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Carr, Frances PhD; Nicholson, Diarmuid PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $70,849 Previous FYs: $ 0 Total: $ 70,849

STUDY OBJECTIVE

To study the hormonal regulation of the vitamin D receptor (VDR) in human breast cancer cells to determine if changes in this receptor augments or decreases the antiproliferative effect of calcitriol.

TECHNICAL APPROACH

Quantitative PCR and hormone binding assays will be used to determine the effects of several hormones, known to regulate the VDR in other tissues, on the concentration of the VDR in human breast cancer cells. The active hormonal treatments will be used to regulate the VDR when testing the antiproliferative effects of calcitriol.

PRIOR AND CURRENT PROGRESS

MRDC awarded funds for this project in October 1992. A lab employee to conduct this study have not been hired, despite repeated attempts to work with CPO to fill the position. To date, four applicants have been referred by CPO, but none were qualified. Thus, no laboratory work has been accomplished.

CONCLUSIONS

None.

REPORT DATE: 03/18/93 WORK UNIT # 1344-92

DETAIL SUMMARY SHEET

TITLE: The Vascular Endothelium: A Critical Site of Toxin Action

KEYWORDS: mammary arteries, nitric oxide

PRINCIPAL INVESTIGATOR: Taylor, Thomas COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the responses of internal mammary artery rings to nitric oxide before and after exposure to the toxin.

TECHNICAL APPROACH
Rings will be cut from internal mammary tissue. These rings will then be hung in a 37 C tissue bath. Response to physiological stimuli will be studied and recorded.

PRIOR AND CURRENT PROGRESS
Tests have been done on tissue from three patients. The tests done on the tissue of two of these patients have been conclusive. However, more tissue will have to be tested before data can be statistically significant.

CONCLUSIONS
None. A larger number of tissue samples from another site are needed.

REPORT DATE: 03/15/93 WORK UNIT # 1345-92

DETAIL SUMMARY SHEET

TITLE: Growth Factors and Mammary Epithelial Cells: Effects of TGF- , TGF-B, Estrogen, and Antiestrogens on Endothelin Secretion and Endothelin Receptors in Breast Cancer Cell Lines and Human Breast Cancer Cells in Primary Culture

KEYWORDS: breast cancer, endothelin

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu PhD.

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assay endothelin (ET) concentrations in media from primary cultures of normal and malignant mammary epithelial cells. To study if TGF-beta or TGF-alpha modulates ET secretion in primary mammary cells and breast cancer lines. To evaluate if estrogen and antiestrogens modulate ET secretion in estrogen receptor positive cells, and to study ET binding to breast cancer cells that will indicate a possible autocrine role for the ET.

TECHNICAL APPROACH

Human breast cancer cell lines will be cultured according to the published procedures in appropriate media, and primary cancer cells will be established from surgically removed malignant breast tissues. Breast cancer cells will be cultured in media alone or with one of the following factors: TGF-alpa, TGF-beta, estrogen, or antiestrogen, for a defined period of time. Media will be removed and assayed for ET concentrations using RIA. Viable cancer cells will also be assayed for ET receptors by competitive Scatchard binding assays using I-125 labelled ET.

PRIOR AND CURRENT PROGRESS

This protocol was not funded by the United States Army Medical Research and Development Command. Hence, the protocol has never been activated, and no study has been done on this project.

CONCLUSIONS

None.

REPORT DATE: 04/15/93 WORK UNIT # 1346-92

DETAIL SUMMARY SHEET

TITLE: Development of a Quantitative Polymerase Chain Reaction for Vitamin D Receptor mRNA

KEYWORDS: mRNA, receptor, cholecalciferol

PRINCIPAL INVESTIGATOR: Nicholson, Diarmuid Ph.D., DAC
ASSOCIATES: Duncan, William LTC MC; Wray, H. Linton COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $12,398 Previous FYs: $ 0 Total: $ 12,398

STUDY OBJECTIVE

To develop a quantitative polymerase chain reaction (PCR) technique for measuring vitamin D receptor (VDR) mRNA; and to utilize this technique to investigate the ontogenesis at the transcriptional level of the hepatic and renal VDR in male and female rats.

TECHNICAL APPROACH

Total RNA is isolated from the tissues by extraction in the presence of phenol and denaturants. The VDR is detected by PCR amplification with VDR specific primers. The amplification is quantified by the inclusion of a synthetic DNA with the same VDR primer sites. Two PCR products are made, authentic and synthetic VDR, which differ in size and can be separated and quantified on a sizing gel. The protocol has been modified to include fluorescence as a detection method.

PRIOR AND CURRENT PROGRESS

The internal VDR standard has been assembled from different oligonucleotide sub-fragments and the artificial gene region was incorporated from the virus PhiX174. The standard has been partially sequenced to verify the construction. Currently the PCR technique is being validated to show that there is a linear response to starting template concentration. The detection method is being evaluated to see which is the most sensitive and reproducible. Fifteen animals were ordered in the last year, and 12 have been euthanized. There were no serious and/or unexpected adverse reactions.

CONCLUSIONS

An internal standard has been shown to work in the system. Both authentic and synthetic VDR can be detected in a single PCR tube. Attaching a fluorescent label to one of the primers and detecting the product on an automated sequencer seems to offer advantages over detection and quantitation by radiolabeling one of the primers.

REPORT DATE: 04/06/93 WORK UNIT # 1347-92

DETAIL SUMMARY SHEET

TITLE: Adrenal Suppression During the Use of Dexamethasone Mouthwash: An Analaysis of Prevalence, Dose-Response Relatinship and Clinical Consequences

KEYWORDS: adrenal, suppression, dexamethasone

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess adrenal reserve in patients using oral dexamethasone mouthwash, and to compare results of the ovine corticotropin releasing hormone (CRH) stimulation test to adrenocorticotropic hormone (ACTH) stimulation testing.

TECHNICAL APPROACH
CRH stimulation test and ACTH stimulation test will be performed on each participant.

PRIOR AND CURRENT PROGRESS
The supplier of the investigational drug CRH has withdrawn this agent from investigational use due to upcoming FDA approval and commercial release. Hence, this protocol has been terminated.

CONCLUSIONS
Protocol terminated due to withdrawal of investigational drug CRH.

REPORT DATE: 05/05/93 WORK UNIT # 1348-92

DETAIL SUMMARY SHEET

TITLE: Combined Free Thyroxine and Sensitive TSH Testing in a Large Clinical Practice: Comparison with Conventional Thyroid Laboratory Testing in Patients with Various States of Thyroid Function and Acquired Binding Protein Abnormality

KEYWORDS: combined, free, thyroxine

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ, MC
ASSOCIATES: Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the utility of a new thyroid hormone profile to that of a classic profile.

TECHNICAL APPROACH
Each of four thyroid function tests or derived indices (in the three clinical states of hyperthyroidism, euthyroidism, and hypothyroidism) will be assessed for discordance rates from the remaining three tests.

PRIOR AND CURRENT PROGRESS
Data has been obtained on 261 patients with miscellaneous thyroid and non-thyroid conditions.

CONCLUSIONS
Pending completion of data analysis.

REPORT DATE: 05/05/93 WORK UNIT # 1349-92

DETAIL SUMMARY SHEET

TITLE: Acute Changes in Total and Free Thyroid Hormone Levels Following Radioiodine Ablation Therapy in the Treatment of Graves' Disease

KEYWORDS: ablation, changes, Graves'

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 7,776 Previous FYs: $ 0 Total: $ 7,776

STUDY OBJECTIVE

To assess for acute changes in free and total thyroid hormones following the discontinuation of antithyroid drugs and administration of radioiodine (I-131) in Graves' disease (GD).

TECHNICAL APPROACH

Patients with GD are admitted to the Kyle Metabolic Unit. Following baseline laboratory testing, antithyroid therapy (ATD) is stopped. Serial blood specimens are obtained for the 6 days preceding and 2 weeks following I-131 ablation.

PRIOR AND CURRENT PROGRESS

Fifteen patients have been enrolled. There have been no serious or unexpected adverse reactions. Preliminary analysis of results on the first 12 patients shows a significant elevation in thyroid hormones following discontinuation of ATD which is not appreciably worsened with the administration of I-131. Correlation between extent of exacerbation after ATD discontinuation and patient characteristics will be performed when the target number of patients have been evaluated.

CONCLUSIONS

Preliminary analysis of data to date suggests that the primary danger of hyperthyroidism exacerbation in patients with GD occurs following preparation for I-31 rather than from the ablation therapy itself.

REPORT DATE: 08/11/93 WORK UNIT # 1350-92

DETAIL SUMMARY SHEET

TITLE: The Effect of Etidronate on Bone Mienral Density (BMD) in Patients on Levothyroxine Suppression

KEYWORDS: cyclical etidronate, bone mineral density

PRINCIPAL INVESTIGATOR: Bernet, Victor CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effects of short and intermediate term therapy with cyclical etidronate on bone mineral density and bone turnover in patients receiving levothyroxine for suppression of nodular thyroid disease or thyroid cancer.

TECHNICAL APPROACH
Patients will be stratified according to the covariates (1) menopausal status and (2) time on levothyroxine. Patients will be randomized to either etidronate treatment or no etidronate treatment. Randomization will be determined using every WRANDOM program. Patients will be evaluated at baseline and 6 months, for a total of 24 months, by BMD, T3RIA, FT4, TSH, ionized calcium, PTH, osteocalcin, as well as 24 hour hydroxyproline, calcium, Pyridinium cross-links and creatinine.

PRIOR AND CURRENT PROGRESS
To date, 57 patients have been enrolled during the first year of the study. The total goal is 90. There have been no serious or unexpected adverse reactions. There have been three withdrawals. One patients developed cataracts, and another had weight gain. Both of these patients were receiving etidronate, but there was no evidence that the problems were related to this therapy. One other patient was enrolled but dropped out prior to the first baseline evaluation. Presently it cannot be determined whether a benefit exists for patients on etidronate therapy.

CONCLUSIONS
More data needs to be collected before any interim or final conclusions can be drawn.

REPORT DATE: 07/07/93 WORK UNIT # 1356-84

DETAIL SUMMARY SHEET

TITLE: Ketoconazole-Induced Suppression of Serum Testosterone Levels in Men

KEYWORDS: ketoconazole, testosterone, gonadotropins

PRINCIPAL INVESTIGATOR: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jul 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 4,352 Total: $ 4,352

STUDY OBJECTIVE
To determine whether the stimulation of serum LH and FSH that follows the ketoconazole-induced reduction in serum testosterone is useful as a test of pituitary gonadotropin reserve.

TECHNICAL APPROACH
Subjects are given ketoconazole 200 mg every 8 hours for 7 days, and serum LH, FSH, testosterone, and 17-OH-progesterone are measured before and after drug administration.

PRIOR AND CURRENT PROGRESS
No new patients were studied during the past year. This protocol is being terminated due to expiration of 5-year time limit.

CONCLUSIONS
Ketoconazole reduces serum testosterone and increases serum LH and FSH.

REPORT DATE: 02/08/93 WORK UNIT # 1359-85

DETAIL SUMMARY SHEET

TITLE: Newer Investigations into the Immune Mechanisms of Thyroid Disease (1985)

KEYWORDS: immunology, thyroid disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Feb 1985

FUNDING: Current FY: $16,699 Previous FYs: $ 51,726 Total: $ 68,425

STUDY OBJECTIVE

To define the T and B cell abnormalities in patients with thyroid disease, both in the peripheral mononuclear cells, as well as in the intra-thyroidal mononuclear cells.

TECHNICAL APPROACH

There are various aspects of this study: 1) Peripheral mononuclear cells are isolated and cultured in the presence of antigen specific and non-specific stimuli; 2) Similar studies are performed with intra-thyroidal cells; 3) Genes encoding unique or interesting cellular proteins are characterized; and 4) Antigen-specific proteins are characterized.

PRIOR AND CURRENT PROGRESS

Clones of cells have been isolated and their antigen-specific characteristics studied. Thyroglobulin clones that are thought to be important in disease propagation have been sequenced using hybridoma antibodies. Several clones have been sequenced and their nucleotide pattern identified. Forty-five patients have been studied with no adverse reactions. Fifteen patients were enrolled in 1992.

CONCLUSIONS

Graves' disease is an autoimmune disease in which there is a heterogeneous activation of T and B cells. Thyroglobulin epitopes have been identified.

REPORT DATE: 11/09/92 WORK UNIT # 1371-86

DETAIL SUMMARY SHEET

TITLE: Transplantation Antigens on Spermatozoa

KEYWORDS: transplantation, HLA, spermatozoa

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Servi e APPROVAL DATE: Nov 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 11,403 Total: $ 11,403

STUDY OBJECTIVE
To determine the nature and amount of transplantation antigens in spermatozoa.
To compare transplantation antigens in blood cells and sperm.

TECHNICAL APPROACH
Detection of transplantation antigens in spermatozoa by use of specific antisera and fluorescent detection techniques. Detection of released antigens by means of hemolytic plaque assay.

PRIOR AND CURRENT PROGRESS
Current work is directed toward using DNA probes to identify specific substances in spermatozoa. One study was completed using an older methodology, and presently a newer method is in use. Progress during the past year has been greatly hampered by difficulty obtaining appropriate sperm specimens, as well as significant limitations in personnel time to perform these studies.

CONCLUSIONS
Deferred, pending completion of current experiments with newer methodology.

REPORT DATE: 11/09/92 WORK UNIT # 1372-86

DETAIL SUMMARY SHEET

TITLE: Effect of Altered Energy Balance on Sexual Maturation in Rats

KEYWORDS: energy balance, sexual maturation, hyperthyroidism

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Nov 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 68,391 Total: $ 68,391

STUDY OBJECTIVE
To determine the effect of alterations in energy balance on sexual maturation in rats.

TECHNICAL APPROACH
Energy balance will be manipulated in rats by food restriction, hyperthyroidism, or catecholamine infusion. Parameters of puberty and growth will be monitored serially, including assessment of such factors as hormone levels, growth rates, timing of vaginal opening, and sperm production.

PRIOR AND CURRENT PROGRESS
There is no additional progress to report since the last APR. This protocol is being closed at the request of DCI because it has reached the maximum permissible time limit for an animal protocol. Additional studies are contemplated, and a new protocol will be submitted.

CONCLUSIONS
Mild hyperthyroidism in weanling rats seems to delay puberty by interfering with hypothalamic function, specifically estrogen induced LH release. Effect of hyperthyroidism on tissue-specific expression of IGF-1 remains to be determined.

REPORT DATE: 04/27/93 WORK UNIT # 1376-86

DETAIL SUMMARY SHEET

TITLE: Ketoconazole Effects on Vitamin D in Hypercalcemic Patients

KEYWORDS: ketoconazole, hypercalcemia, vitamin D

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 18,811 Total: $ 18,811

STUDY OBJECTIVE
To determine whether ketoconazole can reduce serum vitamin D levels and/or serum calcium levels in hypercalcemic patients, and to assess whether such reduction might be of diagnostic or therapeutic use.

TECHNICAL APPROACH
Measurement of serum calcium, PTH, and vitamin D metabolites in hypercalcemic patients before and after administration of ketoconazole 200 mg every 8 hours for 1 week.

PRIOR AND CURRENT PROGRESS
No patients were studied during this fiscal year due to the lack of suitable patients, resources, and time. No additional assays were completed during this fiscal year.

CONCLUSIONS
Ketoconazole lowers serum concentrations of 1,25 dihydroxy-vitamin D in normal and hypercalcemic subjects.

REPORT DATE: 10/19/92 WORK UNIT # 1385-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Thyroid Disease

KEYWORDS: molecular, thyroid, biology

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Wartofsky, Leonard COL MC; Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 65,494 Total: $ 65,494

STUDY OBJECTIVE

To clone the genes encoding for TSH receptor and TSH receptor antibody, and to characterize the receptor gene product.

TECHNICAL APPROACH

This study will try to clone the TSH receptor and related proteins via two different methods. The first involves setting up a Lambda GT11 cDNA expression library from the thyroid gland and screening expression proteins with TSH receptor antibodies, both polyclonal and monoclonal. The second uses expression PCR with specific primers. SSCE will be used to identify specific abnormal areas, that are then sequenced.

PRIOR AND CURRENT PROGRESS

A total of 40 subjects have been enrolled in this study 2 during the past year. There has been no incidence of unexpected or adverse reactions. These techniques have been used to screen a library. Observations have been that thyroglobulin has immunogenic epitopes and that the TSH receptor is immunogenic in aa352-380. Further, this study is screening for abnormal areas in the oncogenes p53 and PTC in the TSH receptor and for peroxidase, RAS, and actin in related, relevant DNA coding areas.

CONCLUSIONS

The TSH receptor is composed of different transcripts, intrathyroidal lymphocytes from patients with autoimmune disease show a polyclonal heterogeneity, a unique area in the TSH receptor that is immunogenic has been identified, thyroglobulin may have gene abnormalities, and the TSH receptor is normal in these states.

REPORT DATE: 07/07/93 WORK UNIT # 1391-87

DETAIL SUMMARY SHEET

TITLE: Bone Mineral Density (BMD) in Patients with Chronic Renal Failure

KEYWORDS: bone mineral, renal failure

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Gouge, Steven MAJ MC; Moore, Jack LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 814 Total: $ 814

STUDY OBJECTIVE

To correlate bone mineral density measurements at the spine and forearm with clinical and laboratory parameters of patients with chronic renal failure.

TECHNICAL APPROACH

This is a pilot retrospective chart review of patients with chronic renal failure who have had forearm and spine bone mineral density measurements.

PRIOR AND CURRENT PROGRESS

Data collection is completed and analyzed. Results indicate that in chronic renal failure, bone loss is primarily cortical, and that measurement of trabecular bone adds little to the evaluation of patients with chronic renal failure. This finding adds little to the existing medical literature on this subject. Therefore, data collection and analysis is being stopped at this time.

CONCLUSIONS

Forearm densitometry is the test of choice to follow the status of bone mineral density in patients with chronic renal failure.

REPORT DATE: 09/14/93 WORK UNIT # 1395-87

DETAIL SUMMARY SHEET

TITLE: Oncogenes and Thyroid Receptors

KEYWORDS: oncogenes, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Carr, Frances PhD; Baker, James MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 535 Previous FYs: $ 182,360 Total: $ 182,895

STUDY OBJECTIVE

To determine whether oncogenes are expressed variably in thyroid tissue derived from patients with different thyroid diseases. Further, patterns of DNA hybridization will help determine if amplified or rearranged genes exist.

TECHNICAL APPROACH

Nucleotides will be subjected to gel electrophoresis and then transferred to nylon or nitrocellulose. These membranes will then be probed with high specific activity P32 labelled inserts or plasmids. Results will be quantitated visually and by spectrophotometer readings, after autoradiography and development. Abnormal patterns of hybridization may indicate expression abnormalities in RNA or amplification or rearrangement abnormalities in DNA.

PRIOR AND CURRENT PROGRESS

This researcher has been successful in developing and refining techniques to isolate, purify, electrophorese, transfer, and hybridize RNA and DNA. Samples have been obtained from 45 patients altogether; 5 during the past year. There have been no serious or unexpected adverse reactions. The patients studied had thyroid cancer, nodules, and goiter. Using the c-Erb B gene probe the researchers noted that several cell lines have rearranged genes, but none of the thyroid tissue analyzed showed consistent abnormality. C-myc patterns were also examined, and no consistent abnormality was noted. p53 gene mutations have been analyzed. There are specific mutations in several cell lines, but none in differentiated cancer. An estimated one million bases were sequenced in this study.

CONCLUSIONS

Thyroid cell lines may grow by virtue of the fact that they have rearranged genes for growth factors, but other oncogenes, such as c-myc and c-Erb B, probably do not play an integral role in determining how thyrocytes grow and divide. p53 is not abnormal in differentiated cells but is abnormal in cell lines.

REPORT DATE: 12/09/92 WORK UNIT # 1399-87

DETAIL SUMMARY SHEET

TITLE: Growth Factors and the Thyroid Gland

KEYWORDS: human thyroid, EGF, ANP

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu PhD
ASSOCIATES: Wartofsky, Leonard COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $ 8,213 Previous FYs: $ 102,850 Total: $ 111,063

STUDY OBJECTIVE

To determine the role of epidermal growth factor (EGF), atrial natriuretic peptide (ANP) and their respective receptors in the maintenance of cultured human thyroid cells derived from surgically removed thyroids in various diseased states.

TECHNICAL APPROACH

1) Primary thyroid cell culture will be established by digesting human thyroid tissues with collagenase, collecting the thyroid cells, then growing cells in proper plates for experiments. 2) EGF and ANP receptors on thyroid cells will be assayed by Scatchard analysis to determine the number of receptor binding sites and their respective binding association constants. 3) Effects of EGF and ANP on thyroglobulin (Tg) secretion by thyroid cells will be determined by assaying Tg concentration media using ELISA. 4) ANP receptor will be characterized by affinity cross-linking using chemical reagent followed by electrophoresis gel separation.

PRIOR AND CURRENT PROGRESS

More than 35 patients signed a consent form, but only 15 thyroid tissues were provided by the pathologist to be processed for this study. The tissues obtained were leftover after the pathologist had taken sufficient thyroid for diagnosis. No adverse effect was observed on patients, and they did not directly benefit from the study. Cultured thyroid cells were incubated with thyrotropin or transforming growth factor, and cell responses were studied. Cultured medium was assayed for endothelin and thyroglobulin levels. Thyroid cells were also assayed for receptor bindings to radiolabeled endothelin and epidermal growth factor to determine receptor binding sites and affinities.

CONCLUSIONS

Thyroid cells synthesize and secrete endothelin into cultured media. Addition of transforming growth factor-B to medium stimulates endothelin secretion. Endothelin receptors were identified on human thyroid cells, and the receptor number was modulated by transforming growth factor-B and thyrotropin. Thyrotropin stimulated binding of epidermal growth factor to receptors on human thyroid cells.

REPORT DATE: 09/08/93 WORK UNIT # 1812

DETAIL SUMMARY SHEET

TITLE: Oncogenes in Basal Cell Nevus Syndrome, Cowden's Disease and Tore's Disease

KEYWORDS: epidermal growth factor, EGF-R

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: James, William COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess whether there is a relationship between oncogenes and diseases involving multiple skin neoplasms associated with internal malignancies.

TECHNICAL APPROACH

DNA will be isolated from peripheral white blood cells and/or lesional tissue in study patients as per "Molecular Cloning: A Laboratory Manual" by T. Maniatis, et al. DNA samples will then be electrophoresed on agarose gel and hybridized with p32-labelled EGF-R probe after Southern blotting. Homologous areas will be visually assessed via autoradiograms. RNA samples will also be prepared by standard techniques and examined as above. No modifications noted to original protocol.

PRIOR AND CURRENT PROGRESS

A manuscript was sent for publication. The editor required further studies which necessitated the enrollment of 11 new subjects this past year. Altogether, 15 subjects have been enrolled, and there has been no incidence of serious or unexpected adverse reactions. No additional subjects will be enrolled.

CONCLUSIONS

EGF-R does not seem to be perturbed in these disease states.

REPORT DATE: 10/07/93 WORK UNIT # 4299

DETAIL SUMMARY SHEET

TITLE: T-Cell Dysfunction as a Prognosticator for the Development of Autoimmune Thyroid Disease in Microsomal Antibody Positive Postpartum Women

KEYWORDS: thyroiditis, oncogenes, autoimmunity

PRINCIPAL INVESTIGATOR: Fein, Henry LTC MC
ASSOCIATES: Smallridge, Robert COL MC; Carr, Frances PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Terminated
APPROVAL DATE: Aug 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 14,018 Total: $ 14,018

STUDY OBJECTIVE

To evaluate T cell dysfunction to shed light on pathogenesis of Autoimmune Thyroid Disease (AITD). It is anticipated that thyroid microsomal antigen specific stimulation will reveal alterations in postpartum microsomal antibody positive patients which may better explain causes of AITD and identify women who will develop clinical postpartum thyroid disease. T cells will be used from four groups of women: postpartum MAb positive(+) or negative(-); nonpostpartum MAb + or -.

TECHNICAL APPROACH

T cells will be obtained at 0,3,6 mos from postpartum subjects and once from nonpostpartum subjects. IL-1 stimulation will look for nonspecific enhancement of immune function. Baseline and stimulatory measurements of proto-oncogenes c-fos, c-jun, and c-myc, IL-2 production, and cell proliferation via [3H] thymidine incorporation will be made. Intergroup variations in the response of these assays to various stimuli will reflect alterations in T cell function. MAb levels will be analyzed in relation to incremental changes of oncogenes, IL-2 production, and cell proliferation. Gestational alterations in immune system will be reflected by differences in the three test criteria when comparing the four groups.

PRIOR AND CURRENT PROGRESS

This research study has been administratively terminated.

CONCLUSIONS

This research protocol has been administratively terminated.

REPORT DATE: 05/27/93 • WORK UNIT # 9266

DETAIL SUMMARY SHEET

TITLE: The Treatment of Graves' Disease with Anti-Idiotype Therapy Using Intravenous Immunoglobulin

KEYWORDS: Graves' disease, anti-idiotype, IV immunoglobulin

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 23,963 Total: $ 23,963

STUDY OBJECTIVE

To determine if IV immunoglobulin alters thyroid function or antibody levels in patients with Graves' disease.

TECHNICAL APPROACH

Subjects will be infused with 4 grams per kg daily for 3 days. Thyroid hormone levels and TBII and TSI levels before, during, and after the infusion will be determined.

PRIOR AND CURRENT PROGRESS

The three infusions performed were tolerated well by two subjects; the third did not feel well during the infusion. No new patients have been accrued since 1988. There were apparently no major alterations in the parameters measured. The plan was to recruit more patients, but the investigators were unable to do so.

CONCLUSIONS

It does not appear that IV immunoglobulin is a successful treatment of Graves' disease.

REPORT DATE: 09/14/93 WORK UNIT # 9273

DETAIL SUMMARY SHEET

TITLE: Identification and Characterization of Thyroid Autoantigens

KEYWORDS: thyroid, antigen, viral

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Humphrey, Michael CPT MC; Francis, Thomas CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To identify viral-like particles in serum or thyroid tissue from patients with thyroid disease.

TECHNICAL APPROACH
Northern and Southern blots with viral probes, as well as PCR with viral and related particles, EB virus transformation, and hybridoma fusions for T and B cells are to be performed.

PRIOR AND CURRENT PROGRESS
Clones were identified that had sequences similar to thyroglobulin, and the sequences were assessed. The thyroglobulin clones were also identified by use of disease-associated monoclonal antibodies in animals. In addition, the T cells that respond to local thyroid autoantigens were characterized. These cells seemed to respond to a particular portion of the TSH receptor (aa 90-120). Spectometry was used to analyze disease-associated antigens. HIV-line viral particles were not found. Dr. Bhata, who was working on this project, has left, so progress was hindered.

CONCLUSIONS
The TSH receptor contains a unique immunogenic portion which can stimulate T cells specifically.

REPORT DATE: 09/03/93 WORK UNIT # 1401

DETAIL SUMMARY SHEET

TITLE: The Effect of Normalization of Intraesophageal pH on Mucosal Proliferation in Barrett's Esophagus

KEYWORDS: Barrett's esophagus, gastroesophageal reflux, proliferation

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 635 Previous FYs: $ 6,597 Total: $ 7,232

STUDY OBJECTIVE

Barrett's esophagus (BE) is a columnar epithelium with premalignant potential which develops in response to prolonged and severe gastroesophageal reflux (GER). The study objective is to normalize the intraesophageal pH with omeprazole (Losec) and then observe the effect on mucosal proliferation as assessed by ornithine decarboxylase activity and thymidine uptake.

TECHNICAL APPROACH

Patients (10) with BE, who have reflux by 24 hour ambulatory esophageal pH study, will have esophagogastro-duodenoscopy (EGD) to obtain biopsies of BE to measure mucosal proliferation rate. Losec 20 mg po bid will be started; a pH study will be repeated after 1 week. If the esophageal pH is still <4, the dosage of Losec will be increased and the pH study repeated. When the esophageal pH is >4 on repeat pH study, the Losec will be continued an additional 60 days. EGD with biopsies and pH study will be completed after 30 and 60 days on Losec. Five control patients (with gastric ulcers) will undergo three sequential EGD's with at least one pH study to exclude GER.

PRIOR AND CURRENT PROGRESS

A total of 10 patients, none during the past year, have been enrolled and have completed this study. There have been no adverse reactions in any patient during the study. The enrollment phase of this study is completed. Progress continues in processing esophageal biopsies and in calculating proliferation indices of tritiated thymidine studies on 1,100 tissue slides generated.

CONCLUSIONS

High dose (40-60 mg) Prilosec, formerly named Losec, normalizes intraesophageal pH in patients with Barrett's esophagus. A decrease in ornithine decarboxylase activity (ODC) was noted following normalization of intraesophageal pH.

REPORT DATE: 12/15/92 WORK UNIT # 1404

DETAIL SUMMARY SHEET

TITLE: Treatment of the Microscopic Colitis/Collagenous Colitis Syndrome with Sulfasalazine: A Double-Blind Crossover Controlled Trial

KEYWORDS: microscopic/collagenous, colitis, sulfasalazine

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 100 Total: $ 100

STUDY OBJECTIVE
To determine whether sulfasalazine is effective therapy for the microscopic colitis/collagenous colitis (MC/CC) syndrome.

TECHNICAL APPROACH
A retrospective review and a prospective, double-blind, placebo controlled crossover study of the efficacy of 12 weeks' treatment with oral sulfasalazine in patients with the MC/CC syndrome.

PRIOR AND CURRENT PROGRESS
Previously, 14 patients suspected to have the MC/CC syndrome had been reviewed to better define the population prior to the prospective trial. Patients with inflammation of the lamina propria (4/14) had greater clinical disease and stool weight. Sulfasalazine appeared to be effective in achieving a clinical response in selected patients. Four patients were enrolled to the prospective arm of the study but did not fulfill histologic criteria for randomization to treatment. During the last year, no additional patients were enrolled in the protocol. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
The MC/CC syndrome causes chronic diarrhea. Histologic features correlate with clinical disease. Sulfasalazine appears to be effective in selected patients.

REPORT DATE: 03/15/93 WORK UNIT # 1406

DETAIL SUMMARY SHEET

TITLE: Campylobacter Pylori: Serologic Studies as a Measure of Efficacy of Treatment

KEYWORDS: helicobacter pylori, peptic ulcer, gastritis

PRINCIPAL INVESTIGATOR: Cheney, Christopher LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 1,116 Previous FYs: $ 10,467 Total: $ 11,583

STUDY OBJECTIVE

a) To determine if H. pylori is a chronic infection; b) to determine efficacy of treatment and whether antibody levels fall with successful eradication of H. pylori; and c) to determine if salivary antibodies are present in detectable amounts to predict infection with the organism.

TECHNICAL APPROACH

Patients known or suspected of harboring H. pylori undergo upper endoscopy with gastric biopsy to confirm the presence of the organism. A tube of blood is drawn and saliva is collected for determination of antibody to the organism. If the organism is present, treatment with Pepto Bismol, tetracycline, and metronidazole is given for 3 weeks. Patients return 1 month and 6 months later for reevaluation.

PRIOR AND CURRENT PROGRESS

Twenty-four patients have been accessioned into the protocol this past year, for a total of 89 patients enrolled to date. Of the new 24 patients, 21 were H. pylori positive and underwent therapy. Of these patients, two were treatment failures. There were no withdrawals or serious or unexpected adverse reactions.

CONCLUSIONS

Treatment continues to have good efficacy (82% eradication). Results of serum and salivary antibody levels have been published and showed declining levels with treatment. Salivary levels are small, and a newer collection method is being used to improve antibody recovery.

REPORT DATE: 04/15/93 WORK UNIT # 1407

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Pneumatic Dilations in the Treatment of Achalasia

KEYWORDS: achalasia, pneumatic dilation

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study the efficacy of pneumatic dilations performed in patients at WRAMC; and to determine if manometric or esophageal emptying studies can predict success of dilation.

TECHNICAL APPROACH

Review charts of patients evaluated for achalasia in the GI Clinic at WRAMC. Data collection will include patient's symptoms and weight, esophageal manometry studies, and esophageal emptying studies prior to and 1 month after dilation.

PRIOR AND CURRENT PROGRESS

Thirty charts of previously untreated achalasia patients have been reviewed; none this past year. Data collected includes the results of esophageal manometry studies and cornflakes emptying studies performed before dilation and at 1, 6, and 12 months after dilation. Additionally, several parameters were measured at the time of dilation. A manuscript is in progress.

CONCLUSIONS

Graduated pneumatic dilation is a safe and effective treatment for achalasia. No perforations were noted in 75 dilations performed. No single parameter examined at the time of dilation could indicate success versus failure. Significant improvement in post-dilation parameters was noted in successfully treated patients.

REPORT DATE: 05/26/93 WORK UNIT # 1408

DETAIL SUMMARY SHEET

TITLE: Nocturnal Gastroesophageal Reflux--Factors Associated with Reflux Events: A Retrospective Review of 24 Hour Esophageal pH Monitoring Data

KEYWORDS: nocturnal, gastro[illegible]l reflux, 24 hr pH monitoring

PRINCIPAL INVESTIGATOR: Landes, Tim MAJ MC
ASSOCIATES: Maydonovitch, Corinne BS; Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review 24 hr pH monitoring studies to identify behavioral and physiologic events associated with gastroesophageal reflux (GER) events.

TECHNICAL APPROACH
Review 24 hr pH studies performed in the WRAMC GI Clinic over the past 4 years to select two groups: 1) patients with significant GER, as defined by a monitoring score >20; and 2) a control group, patients evaluated for GER who had a score </=20. Reflux events in each group will be analyzed for time of day they occurred, relationship to meals, patient's posture, and duration of reflux episode.

PRIOR AND CURRENT PROGRESS
A total of 220 24-hour pH charts were reviewed for this study; 156 of them during this past year. Data was collected from 176 of these charts: 64 charts of patients with supine GER and 112 charts of patients with upright reflux. Currently, data is being collated and analyzed in preparation of two manuscripts.

CONCLUSIONS
Lower esophageal sphincter pressure does not predict degree of acid exposure in the supine position. Upright reflux patients have the majority of reflux episodes within 2 hours after a meal.

REPORT DATE: 10/15/92 WORK UNIT # 1410

DETAIL SUMMARY SHEET

TITLE: Open Label Trial of Low Dose Oral Pulse Methotrexate Therapy for Primary Sclerosing Cholangitis

KEYWORDS: methotrexate, sclerosing, cholangitis

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC
ASSOCIATES: Peller, Thomas MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine possible efficacy of low-dose methotrexate in the treatment of primary sclerosing cholangitis.

TECHNICAL APPROACH
After baseline evaluation to rule out other potential etiologies of liver disease, the patient has an ERCP, liver biopsy, and HIDA scan. They are then placed on gradually increasing doses of methotrexate (up to a maximum dose of 25 mg weekly). The patients are followed on a monthly basis. At the end of 1 year, a total re-evaluation is performed, with treatment continued for an additional year.

PRIOR AND CURRENT PROGRESS
A total of 10 patients have been entered into the study; 4 this past year. Three have completed the full 2 years and are being followed clinically. One subject refused to continue the protocol after 13 months; the drug was discontinued, and the patient is being followed by a primary physician. Two patients have failed therapy after 13 and 18 months, respectively. One has received a liver transplant and is doing well. The second is awaiting transplant. The remainder are continuing with the protocol.

CONCLUSIONS
Study is ongoing, and additional subjects are being recruited.

REPORT DATE: 01/22/93 WORK UNIT # 1411

DETAIL SUMMARY SHEET

TITLE: The Effect of Lithium Carbonate on Gastric Emptying and Gastrointestinal Hormones in Humans: A Double Blind Randomized Study

KEYWORDS: lithium, carbonate, gastric emptying

PRINCIPAL INVESTIGATOR: DeMarkles, Michael CPT MC
ASSOCIATES: Wong, Roy COL MC; Sjogren, Robert COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,510 Total: $ 1,510

STUDY OBJECTIVE

To study the effect of lithium carbonate on gastric emptying and gastrointestinal hormones in humans.

TECHNICAL APPROACH

Twenty patients will be given either placebo or lithium carbonate (300 mg PO Q3hrs X 10 doses). A gastric emptying study with a concurrent electrogastrogram will be done after each medication. Gastric hormone and lithium levels will be drawn during the study.

PRIOR AND CURRENT PROGRESS

Seven patients have been completed; none this past year. No serious or unexpected adverse events have occurred, and none of the volunteers have had to withdraw. There has been no benefit to the patients.

CONCLUSIONS

Lithium carbonate does not appear to effect gastric emptying or gastrointestinal hormone levels in humans.

REPORT DATE: 02/28/93 WORK UNIT # 1412

DETAIL SUMMARY SHEET

TITLE: Clinical and Serologic Evaluation of Blood Donors at Walter Reed Army Medical Center

KEYWORDS: hepatitis C antibody, blood donors

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
(1) To survey blood donors for the prevalence of hepatitis C antibody, and (2) to determine the prevalence of chronic hepatitis in blood donors who are rejected for donation due to the presence of increased ALT/presence of hepatitis B core antibody.

TECHNICAL APPROACH
To determine the prevalence of hepatitis C antibody, blood donors (at the time of donation) will provide an additional sample of blood to be tested for the presence of hepatitis C antibody. The antibody studies will be performed in Dr. Sjogren's lab at WRAIR. To determine the significance of abnormal ALT or hepatitis B core antibody, blood donors with such an abnormality will be invited via mail to participate in the study.

PRIOR AND CURRENT PROGRESS
Records of 7921 consecutive blood donors were screened for hepatitis C; none this past year. There were no serious or unexpected side effects from the study. Eighteen civilian and 25 military blood donors were found to have detectable anti-hepatitis C virus (anti-HCV). Of those donors, a greater percentage of civilians (44%) vs military (12%) also tested positive for hepatitis B core antibody (HBcAb).

CONCLUSIONS
Military donors with anti-HCV had lower prevalence of HBcAB compared to civilian donors. Sporadic transmission of HCV in the military appears to be proportionately higher than in the civilian population.

REPORT DATE: 02/15/93 WORK UNIT # 1413

DETAIL SUMMARY SHEET

TITLE: Large Bowel Adenomatous Polyp Dietary Intervention Study-Clinical Centers

KEYWORDS: colon polyps, fat, fiber

PRINCIPAL INVESTIGATOR: Kikendall, J. Walter COL MC
ASSOCIATES: Mateski, Donna MS RD; Murphy, Joseph MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 5,053 Previous FYs: $ 34,319 Total: $ 39,372

STUDY OBJECTIVE

1) To determine whether a high fiber, low fat diet can reduce the recurrence of colonic adenomas; 2) To determine whether the diet modulates several putative intermediate markers of carcinogenesis (ODC activity, PCN antigen, labeling index); and 3) To determine the degree of correlation between recurrence of adenomas and modulation of markers.

TECHNICAL APPROACH

WRAMC is one of eight centers. Each center enrolls healthy subjects who have recently undergone colonscopic removal of all adenomas. Subjects are randomized to no intervention or to a low fat, high fiber, high fruit and vegetable diet. Subjects randomized to diet are intensively counselled. Colonoscopy is repeated at 1 and 4 years, and all polyps are removed and examined histologically. Unprepped sigmoidoscopy is performed at entry, 1, and 4 years to obtain mucosal samples for analysis for intermediate endpoints. Blood specimens and diet and health questionnaires are collected on an annual basis.

PRIOR AND CURRENT PROGRESS

Since the last APR, 70 more subjects have been enrolled. As of February 1993, a total of 107 subjects have been enrolled. Of these, 93 also consented to participate in the intermediate endpoint sub-study. Another 39 people had one or two visits but were ineligible and not enrolled. Recruitment expanded to DeWitt ACH (Mar 92), Kimbrough ACH (May 92), and Malcolm Grow AFMC (Nov 92). Nutrition counseling occurs at WRAMC, Ft. Meyer, Ft. Belvoir, Ft. Meade, Ft. Detrick, Ft. Ritche, Vint Hill Farms, and Andrews AFB. All subjects receive follow-up for adenomas. Intervention subjects receive the benefits of a diet compatible with guidelines of major health groups. There have been no serious or unexpected adverse reactions. One subject died of an unrelated cause.

CONCLUSIONS

It is too early to draw any conclusions, as our earliest randomized subjects are only 1 year into their 4 year period of participation.

REPORT DATE: 03/02/93 WORK UNIT # 1414

DETAIL SUMMARY SHEET

TITLE: Case Control Study of Colonic Adenomas

KEYWORDS: colonic adenomas, risk factors, carotenoids

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 710 Previous FYs: $ 28,537 Total: $ 29,247

STUDY OBJECTIVE
To analyze previously collected data to define risk factors for colonic neoplasia. An amendment provides for analysis of frozen serum samples for gastrin, IGF-1, and 1,25-OH vitamin D.

TECHNICAL APPROACH
Three hundred and sixty-one subjects undergoing colonoscopy donated blood and urine samples and completed a dietary and environmental questionnaire from 1983-1987.

PRIOR AND CURRENT PROGRESS
Due to funding shortages, computer input of collected data has been slow. All data with the exception of the dietary data has now been entered into a computer data base. Because of the enormous size of the data base, it was necessary to employ a mainframe computer in Baltimore. Dr. Patricia Langenberg, one of the study investigators, will analyze the data in collaboration with the PI. This will tentatively be accomplished in the late summer, 1993. Some preliminary analyses have been performed on a personal computer and have resulted in several publications.

CONCLUSIONS
Cigarette smoking and alcohol consumption are independent risk factors for colonic adenomas. Serum gastrin, IGF-1, and 25-OH vitamin D levels are similar in subjects with adenomas and colonoscopy-negative controls.

REPORT DATE: 04/15/93 WORK UNIT # 1415

DETAIL SUMMARY SHEET

TITLE: The Compassionate Use of Cisapride in the Treatment of Patients with Refractory Nonulcer Dyspepsia, Diabetic Gastropareseis with Intolerance to Metoclopramide and Chronic Intestinal Pseudo-obstruction

KEYWORDS: Cisapride, non-ulcer dyspepsia, diabetic gastroparesis

PRINCIPAL INVESTIGATOR: Sjogren, Robert COL MC
ASSOCIATES: Shay, Steven COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To treat patients with refractory non-ulcer dyspepsia, diabetic gastroparesis, and intestinal pseudo-obstruction with Cisapride, a prokinetic agent not yet approved by the FDA.

TECHNICAL APPROACH

Patients are treated with 20 mg PO and tid of Cisapride. Short-term treatment for 6 weeks is initiated. If symptomatic improvement occurs, the medication is continued long-term, as long as improvement continues. Appropriate blood tests and urinalysis are periodically obtained.

PRIOR AND CURRENT PROGRESS

One patient has been enrolled and has been on Cisapride 20 mg tid for 20 months without adverse effect. Symptoms of refractory non-ulcer dyspepsia are markedly improved.

CONCLUSIONS

Cisapride may be effective in selected cases of non-ulcer dyspepsia.

REPORT DATE: 05/26/93 WORK UNIT # 1416

DETAIL SUMMARY SHEET

TITLE: Association of Acromegaly and Intermediate Markers of Neoplasia

KEYWORDS: acromegaly, colonic neoplasia

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC
ASSOCIATES: Schaaf, Marcus MD; Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 635 Previous FYs: $ 1,908 Total: $ 2,543

STUDY OBJECTIVE

To find the prevalence of colonic neoplasia in acromegalics, to identify risk factors, and to determine if there is a correlation between disease activity in acromegaly and intermediate markers of mucosal proliferation (ODC activity and tritiated thymidine uptake).

TECHNICAL APPROACH

Patients will have serum drawn for somatomedin C levels, undergo flexible sigmoidoscopy to obtain rectal tissue to measure ODC activity and tritiated thymidine uptake, and receive a colonoscopy to survey for colonic neoplasia.

PRIOR AND CURRENT PROGRESS

A total of 34 patients with acromegaly and 14 control patients have been enrolled and completed the study. No new patients were recruited this past year. No serious or unexpected adverse reactions were noted. Benefits to patients included diagnosis of adenomatous polyps in 15 patients and adenocarcinoma of the colon in 3 patients. No new patients are expected to be recruited into this study. A manuscript is in progress.

CONCLUSIONS

There is a higher prevalence of colonic neoplasia in patients over age 50 years of age with acromegaly compared to heme (+) stool patients. There is a significant correlation between tritiated thymidine uptake in colonic mucosa and serum somatomedin C.

REPORT DATE: 06/10/93 WORK UNIT # 1417

DETAIL SUMMARY SHEET

TITLE: Incidence of Gastric Mucosal Injury in Patients Ingesting Liquid Versus Solid Ibuprofen

KEYWORDS: gastritis, mucosal injury, ibuprofen

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 20,014 Total: $ 20,014

STUDY OBJECTIVE

To determine if there is a difference in the incidence of gastric mucosal injury between liquid and solid forms of ibuprofen.

TECHNICAL APPROACH

To examine the gastric mucosa endoscopically before and after 3 days of a randomized course of either liquid or solid ibuprofen.

PRIOR AND CURRENT PROGRESS

Eighteen new subjects were enrolled in this study since May 1991. A total of 34 subjects have been enrolled to date. There have been no serious or unexpected reactions to the ibuprofen, and there have been no complications with the endoscopy. All subjects have completed the study with no withdrawals.

CONCLUSIONS

The data (endoscope and histologic examination) shows no significant difference between ingestion of liquid vs. solid ibuprofen in damage to the stomach.

REPORT DATE: 06/14/93 WORK UNIT # 1418

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of 99mTechnetium Sulfur Colloid Liver Spleen Scan and 99mTechnetium Mebrofenin Hepatobiliary Radionuclide Scan for Diagnosis of Diffuse Hepatocellular Disease

KEYWORDS: diffuse liver disease, scintigraphy

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the utility of quantitative liver-spleen and hepatobiliary scintigraphy to liver biopsy for evaluating severity and etiology of hepatocellular abnormalities.

TECHNICAL APPROACH
Patients between 18 and 70 years old suspected of having diffuse liver disease and in whom a liver biopsy is indicated, will be enrolled in the study. To evaluate severity of liver disease a liver-spleen scan, hepatobiliary radionuclide scan, and liver biopsy will be performed, and the results will be compared.

PRIOR AND CURRENT PROGRESS
A total of six patients have been enrolled in this study since its inception in June 1991. Over the preceding 12 months no additional patients were entered. Current Nuclear Medicine personnel shortages preclude further enrollment at this time, but further work will be done as staffing improves. There have been no serious or unexpected adverse reactions, and no patients have been withdrawn from the study.

CONCLUSIONS
Ongoing study.

REPORT DATE: 11/13/92 WORK UNIT # 1420

DETAIL SUMMARY SHEET

TITLE: Household Transmission of Hepatitis C Virus in Military Populations

KEYWORDS: hepatitis C, transmission

PRINCIPAL INVESTIGATOR: Smith, Mark CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the prevalence of hepatitis C virus (HCV) in household members of patients positive for the anti-hepatitis C antibody.

TECHNICAL APPROACH
All subjects with detectable antibody to hepatitis C, as well as control individuals, will undergo an initial medical history, physical exam, and biochemical testing to obtain evidence of chronic liver disease. All individuals will be followed at 3 month intervals for 1 year. The quarterly tests will consist of liver tests and serum virological markers. Subjects found to have clinical and/or biochemical evidence of liver disease will be followed by a gastroenterologist or a pediatrician.

PRIOR AND CURRENT PROGRESS
A total of 42 index patients were enrolled and completed this year. Thirty-six patients were RIBA II. Six of 35 spouses tested were positive, and none of the 17 other household contacts were positive. Two of the six positive spouses had independent risk factors for hepatitis C. There have been no serious or unexpected adverse reactions to any of the subjects involved.

CONCLUSIONS
Results suggest that monogamous sexual contact, but not nonsexual household contact, with anti-HCV positive patients results in a moderately increased risk of hepatitis C.

REPORT DATE: 11/13/92 WORK UNIT # 1421

DETAIL SUMMARY SHEET

TITLE: A Randomized, Controlled Trial of Interferon Alpha and Thymosin Alpha 1 in Patients with Hepatitis C Antibody Positive Chronic Active Hepatitis

KEYWORDS: hepatitis C, interferon alpha, thymosin alpha-1

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 570 Previous FYs: $ 0 Total: $ 570

STUDY OBJECTIVE
To demonstrate efficacy of recombinant interferon alpha-2b in the treatment of eligible subjects with chronic hepatitis C, and to investigate the augmentation of response with interferon using thymosin alpha-1 as an immunomodulator.

TECHNICAL APPROACH
Eligible subjects are randomized to one of three study arms: Treatment with IFA, IFA+TMA-1, or control; up to 40 patients in each group. Patients will begin treatment while hospitalized. Outpatient follow-up will be weekly x 2, biweekly x 3, and monthly thereafter. Patients must undergo liver biopsies within 3 months of study enrollment and within 1 month of completion of the initial 6 months of treatment. Each visit will include a record of side effects, general health assessment, specific problems, and lab work. All patients will be offered definitive therapy.

PRIOR AND CURRENT PROGRESS
A total of six patients have been randomized, with no serious or unexpected adverse reactions. One patient has completed 6 months of treatment.

CONCLUSIONS
None yet to report.

REPORT DATE: 11/13/92 WORK UNIT # 1422

DETAIL SUMMARY SHEET

TITLE: Significance and Natural History of Detectable Hepatitis C Antibody in Military Populations

KEYWORDS: hepatitis C antibody, natural history

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the prevalence of liver disease in a military population with detectable antibody to hepatitis C in serum, and to determine the clinical, biochemical, and histological extent of the liver disease. To better define the risk factors of hepatitis C virus (HCV) infection.

TECHNICAL APPROACH
The study consists of enrolling anti-HCV-positive individuals and control subjects without detectable anti-HCV. All subjects will undergo two serological screenings for liver disease the first 6 months of the study. Subjects having clinical and/or biochemical evidence of chronic liver disease will be referred for follow-up. During the 3 year follow-up period, all subjects (control and study) will be seen at 6 months for a health exam, liver tests, and serum virological markers. Each subject with chronic liver disease will undergo additional studies during the first year.

PRIOR AND CURRENT PROGRESS
Two patients have been enrolled to date. There have been no serious or unexpected adverse reactions to any of the subjects.

CONCLUSIONS
None yet to report.

REPORT DATE: 03/05/93 WORK UNIT # 1423

DETAIL SUMMARY SHEET

TITLE: Intermediate Markers of Colonic Neoplasia

KEYWORDS: colonic adenocarcinoma, screening, intermediate markers

PRINCIPAL INVESTIGATOR: Kikendall, James COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 2,045 Previous FYs: $ 4,718 Total: $ 6,763

STUDY OBJECTIVE
To determine whether colonocyte expression of any of several putative intermediate markers of colonic neoplasia predicts the presence of neoplasia.

TECHNICAL APPROACH
Stool specimens will be collected from patients with colon cancer, patients with colon adenomas, and normal controls. Colonocytes will be harvested from the stool samples and will be tested for several antigens, growth factor receptors, chromosomal and genetic alterations, blood group substances, and lectin binding studies to detect any factors correlating with neoplasia.

PRIOR AND CURRENT PROGRESS
Since the study began, 24 subjects have been enrolled. Patients' clinical diagnoses have ranged from carcinoma to normal, and colonocyte assays are pending. At this time, five new patients are added every 2 weeks according to a pre-arranged schedule with University of Maryland examiners. Regular inflow of patients is virtually assured until completion of the study.

CONCLUSIONS
Forthcoming data will permit conclusions at a later date.

REPORT DATE: 11/09/92 WORK UNIT # 1424

DETAIL SUMMARY SHEET

TITLE: Reproduction of Intraperitoneal (IP) Hypertension During Peritoneal Dialysis: Occurrence and Characterization of IP Hypertension, and Association with Antral-Duodenal-Jejunal Motility Electrogastrogram, and Esophageal pH

KEYWORDS: intraperitoneal, hypertension, dialysis

PRINCIPAL INVESTIGATOR: Shay, Steven COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To reproduce and characterize intraperitoneal hypertension (IPH) during peritoneal dialysis; to study the effect of IPH on antroduodenal-jejunal motility and gastroesophageal reflux.

TECHNICAL APPROACH
Antral-duodenal-jejunal motility, gastric myoelectric activity, intraperitoneal pressure, intrarectal pressure, and intraesophageal pH will be monitored during peritoneal dialysis in patients at baseline and after a standard meal. Measurements will be obtained in a 2-day study, with and without infusion of saline into the intraperitoneal cavity to establish intraperitoneal hypertention.

PRIOR AND CURRENT PROGRESS
No subjects were enrolled into this study this past year. This study is being closed due to retirement of principal investigator.

CONCLUSIONS
No conclusions can be drawn.

REPORT DATE: 07/13/93 WORK UNIT # 1450

DETAIL SUMMARY SHEET

TITLE: Adenomatous Colonic Polyps: A Vitamers and MFO Induction

KEYWORDS: colon polyps, vitamin A, beta-carotene

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC
ASSOCIATES: Burgess, Mary RD; Bowen, Phyllis RD PhD

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Jul 1982

FUNDING: Current FY: $ 0 Previous FYs: $ 16,101 Total: $ 16,101

STUDY OBJECTIVE

a) Case control portion: To evaluate risk factors for colonic adenomas. b) Intervention portion: To evaluate beta-carotene, 15mg po daily, as a colon cancer chemopreventive agent.

TECHNICAL APPROACH

a) Case control portion: Subjects who report for indicated colonoscopy who meet entry criteria are assessed by dietary and historical interview and sampling of blood and urine. Subjects with polyps (adenomas) and colonoscopy-negative controls are compared. b) Intervention Study: Subjects are randomized to receive placebo or beta-carotene after removal of colonic adenomas. Repeat colonoscopy assesses recurrence over the subsequent 3 years. Although beta-carotene is not known to have any harmful side effects, several potential side effects are monitored.

PRIOR AND CURRENT PROGRESS

The intervention was completed in 1990. No serious side effects due to beta carotene were observed. Beta carotene, 15 mg p.o., was determined to be of no benefit in preventing recurrence of colonic adenomas. This was reported at the October 1991 meeting of the American College of Gastroenterology. The only factor found to predict adenoma recurrence was the number of prior adenomas. This was reported at the American Gastroenterology Association Meeting in May 1992. During the past year, data entry for the case-control portion was completed. Plans are to perform data analysis and to begin writing a manuscript(s) in September 1993. Data entry for the intervention study is in progress.

CONCLUSIONS

Beta-carotene, 15mg p.o. qd, does not reduce the recurrence of colonic adenomas. The number but not the size of previous adenomas predicts recurrence. Both alcohol and cigarette use are associated with initial adenomas.

REPORT DATE: 04/14/93 WORK UNIT # 1483

DETAIL SUMMARY SHEET

TITLE: Evaluation of Gastroesophageal Reflux as a Cause of Hoarseness

KEYWORDS: hoarseness, reflux, esophagitis

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Murphy, Joseph MAJ MC; Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 2,340 Total: $ 2,340

STUDY OBJECTIVE

To determine if gastroesophageal reflux (GER) is a cause of "idiopathic" hoarseness.

TECHNICAL APPROACH

Patients with idiopathic hoarseness and characteristic ENT findings undergo standard GI evaluation for GER. If GER is identified, the patient undergoes baseline voice harmonic analysis and is reevaluated after 8 weeks of medical therapy.

PRIOR AND CURRENT PROGRESS

A total of 17 patients referred by the ENT Clinic have been evaluated for gastroesophageal reflux (GER); none this past year. Eleven of these patients agreed to participate in the study, and all have completed participation. There have beeen no withdrawals or adverse reactions. A new protocol is being prepared.

CONCLUSIONS

Of the 11 patients studied, 6 were found to have gastroesophageal reflux and underwent medical therapy. Improvement in esophagitis but not voice harmonics was noted after therapy.

REPORT DATE: 08/03/93 WORK UNIT # 1487

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of the Effect of Medical Therapy on Plasma and Tissue Zinc Levels in Esophagitis

KEYWORDS: zinc, esophagitis, GERD

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Smith, Mark MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Jul 1986

FUNDING: Current FY: $ 635 Previous FYs: $ 1,158 Total: $ 1,793

STUDY OBJECTIVE

To prospectively evaluate the effect of anti-gastroesophageal reflux therapy on plasma and esophageal tissue zinc concentrations; and to determine if a correlation exists between degree of esophageal inflammation and plasma and esophageal zinc concentration.

TECHNICAL APPROACH

Patients with endoscopically proven peptic esophagitis undergo esophageal biopsy and phlebotomy for tissue and serum zinc concentration. After standard medical anti-reflux therapy, tissue and blood specimens are obtained for comparison zinc concentrations.

PRIOR AND CURRENT PROGRESS

A total of 22 patients have been enrolled in this study, with 3 patients enrolled this past year. All patients completed the study with no complications. This study is being closed because it exceeds the 5 year limit for an active protocol.

CONCLUSIONS

Tissue zinc levels significantly decreased following healing of esophagitis with omeprazole. However, serum zinc levels remained low after healing, suggesting a longer period to replace the plasma zinc pool.

REPORT DATE: 10/09/92 WORK UNIT # 1496

DETAIL SUMMARY SHEET

TITLE: The Effects of Non-Steroidal Anti-Inflammatory Drugs on the Secretion of Human Salivary Epidermal Growth Factor

KEYWORDS: epidermal growth factor, saliva, anti-inflammatory drugs

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS; Dutta, Sudhi MD

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 525 Total: $ 525

STUDY OBJECTIVE

To determine if therapeutic doses of non-steroidal anti-inflammatory drugs affect salivary epidermal growth factor (EGF) secretion in humans.

TECHNICAL APPROACH

In a double-blind, randomized manner, volunteer subjects receive, on separate occasions two weeks apart, placebo TID for 3 days or indomethacin, 50 mg TID for 3 days. On the following morning, after a final drug dose, saliva is collected in a centrifuge tube, centrifuged, stored at -70C and analyzed by radioimmunoassay for EGF. Serum samples are collected and analyzed for indomethacin levels.

PRIOR AND CURRENT PROGRESS

A total of 21 subjects have been enrolled in this study. No new subjects were enrolled during this past year. One subject erroneously received placebo twice and was dropped from the study. There were no serious or unexpected adverse reactions related to the study. There is no direct benefit to participation in this study. This study is completed; no more subjects will be enrolled.

CONCLUSIONS

Indomethacin significantly decreases salivary epidermal growth factor.

REPORT DATE: 10/28/92 WORK UNIT # 1497

DETAIL SUMMARY SHEET

TITLE: The Effect of Indomethacin on Rectosigmoid Mucosal Blood Flow and Rectosigmoid Mucosal Prostaglandin Levels in Humans

KEYWORDS: indomethacin, blood flow, laser Doppler

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Pacicco, Thomas MAJ MC; Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 1,250 Total: $ 1,250

STUDY OBJECTIVE

To determine the effect of prostaglandin synthesis inhibition with indomethacin treatment on rectosigmoid mucosal blood flow and rectosigmoid mucosal prostaglandin E2 levels.

TECHNICAL APPROACH

In a double-blind, randomized fashion, each subject will receive, on two separate occasions separated by 2 weeks, either placebo TID for 3 days or indomethacin 50mg TID for 3 days. The morning after the final dose of placebo or indomethacin, rectosigmoid mucosal blood flow will be measured with a laser Doppler probe inserted through the biopsy channel of an endoscope. Two rectal mucosal biopsies will be obtained to measure tissue prostaglandin levels, and a blood sample will be taken to measure indomethacin levels.

PRIOR AND CURRENT PROGRESS

A total of 10 control male subjects have been studied with no serious or adverse effects; 5 subjects from a young age group and 5 from an older age group. Subjects were studied on two separate days to test reproducibility of blood flow measurements via laser Doppler technique. No new subjects have been enrolled this year. Progress on this study has been slow due to technical difficulties which have been resolved and changes in personnel conducting the study. Subjects are being recruited to investigate blood flow with indomethacin treatment.

CONCLUSIONS

Blood flow measurement with laser Doppler is reproducible from day-to-day (r=0.9015). Blood flow measurements did not significantly differ between the two age groups.

• REPORT DATE: 12/09/92 WORK UNIT # 1498

DETAIL SUMMARY SHEET

TITLE: Pathophysiology and Treatment for Non-Ulcer Dyspepsia (Using Cisapride)

KEYWORDS: non-ulcer dyspepsia, irritable bowel syndrome, Cisapride

PRINCIPAL INVESTIGATOR: Cremins, James CPT MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare gastric motility and electrophysiology in patients with non-ulcer dyspepsia vs. normal volunteers. To determine the effect of a prokinetic agent, Cisapride, on symptoms and objective tests in patients with non-ulcer dyspepsia in a double-blind, crossover placebo controlled fashion.

TECHNICAL APPROACH

Patients with dyspeptic symptoms, in whom ulcer has been rigorously excluded, will be studied. Three hour electrogastrograms and 24 hour antral motility evaluations will be performed after treatment with placebo and Cisapride. Changes in symptoms will be measured using a questionnaire. A double-blind crossover design will be employed so that each subject receives both placebo and Cisapride.

PRIOR AND CURRENT PROGRESS

A total of six patients have been enrolled and completed the protocol. No patients were enrolled last year, as the principal investigator was in transition to retirement. There has also been some difficulty enrolling patients with the necessary condition. There have been no serious or unexpected adverse reactions in any of the patients studied.

CONCLUSIONS

None at this time, as the study is a double-blind, placebo controlled study, and more patients are to be enrolled.

REPORT DATE: 09/25/93 WORK UNIT # 2031

DETAIL SUMMARY SHEET

TITLE: Gastrointestinal Blood Loss During Marathon Running and the Effect of Cimetidine on its Prevention

KEYWORDS: GI blood loss, marathon running, cimetidine

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 149 Previous FYs: $ 3,895 Total: $ 4,044

STUDY OBJECTIVE
To determine the frequency and severity of gastrointestinal blood loss during marathon and endurance exercise, and the effects of cimetidine on its prevention.

TECHNICAL APPROACH
Qualitative and quantitative stool hemoglobin analyses are performed before and after runners complete endurance competitive events. A protocol modification was approved in FY91 to allow endoscopy of some participants in order to localize bleeding. An extension for 1 year was submitted. However, it was disapproved by the CIC 11/16/93. A new protocol is required.

PRIOR AND CURRENT PROGRESS
Two 100-mile ultramarathon events have been completed. GI bleeding occurred in the majority of subjects, and symptoms were severe at times. Cimetidine protected runners in the unblinded portion of the study. To date, 30 of the planned 250 marathon runners have been studied (none during this past year), and results show a trend toward improvement when cimetidine is used. Seven runners completed all or part of the modified protocol, including panendoscopy following the maraathon. No complications or untoward effects have been noted. There have been publications and presentations from this data (1990-1991).

CONCLUSIONS
Data suggests cimetidine may be of benefit in improving GI symptoms associated with endurance running and reduction of GI bleeding. Further evaluation and study of this condition is warranted and planned.

REPORT DATE: 11/24/92 WORK UNIT # 1027

DETAIL SUMMARY SHEET

TITLE: Symptoms in the Community: Prevalence, Etiology and Psychiatric Co-Morbidity

KEYWORDS: symptoms, psychiatric, epidemiology

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: General Medicine Service APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To analyze a large data base (Epidemiologic Catchment Area Survey) to determine the community prevalence, patient-attributed etiology, and psychiatric co-morbidity related to common medical symptoms.

TECHNICAL APPROACH
Data base will be used to provide information related to common medical symptoms.

PRIOR AND CURRENT PROGRESS
Data was analyzed using logistic regression analysis. A manuscript has been submitted to the Archives of Internal Medicine.

CONCLUSIONS
Community prevalence of symptoms is very high. Only 20% are considered by patients to be "minor." About 35% of the symptoms are potentially psychiatric in etiology. The presence of any one of the 15 most common symptoms is associated with a two- to threefold increased risk of a concomitant psychiatric order.

REPORT DATE: 08/10/93 WORK UNIT # 1028

DETAIL SUMMARY SHEET

TITLE: Termination of the Physician-Patient Relationship in a Primary Care Clinic

KEYWORDS: primary care, patient satisfaction, continuity of care

PRINCIPAL INVESTIGATOR: Roy, Michael CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: General Medicine Service APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 425 Previous FYs: $ 0 Total: $ 425

STUDY OBJECTIVE
To identify independent predictors of patient satisfaction with the process of transferring their care from a graduating resident physician to a new resident. An addendum is planned to determine whether interventions can improve patient satisfaction.

TECHNICAL APPROACH
An attitudinal survey will be given to consecutive patients returning to the clinic for their first visit with a new physician and will be mailed to patients not returning within 4 months of the physician change. The questions will elicit the patients' degree of satisfaction with the transfer process, as well as potential predictors of satisfaction. Univariate and multivariate analyses will be performed using SAS to identify the independent predictors of patient satisfaction.

PRIOR AND CURRENT PROGRESS
In the past year, 437 patients were enrolled, yielding a total of 813 participants. There were no incidences of serious or unexpected adverse reactions. Benefits to patients included an increase over the previous year in the percentage of patients informed of the transfer of care (70% to 78%) and the percentage of patients satisfied with the handling of the transfer of care (47% to 66%).

CONCLUSIONS
Five predictors of patient satisfaction with the transfer of care were identified, most of which are physician-dependent. Physician-oriented seminars and letters to inform patients of the transfer of care independently increase patient satisfaction.

REPORT DATE: 02/11/93 WORK UNIT # 1029

DETAIL SUMMARY SHEET

TITLE: Common Symptoms in Ambulatory Medicine: The Effects of Attributions and Expectations on Symptom Outcome and Patient Satisfaction

KEYWORDS: somatization, patient satisfaction, patient expectations

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC
ASSOCIATES: Marple, Richard MAJ MC(P); Lucey, Catherine MD

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the prevalence of various concerns and expectations in patients presenting with common physical complaints; the recognition of these concerns and expectations by the physicians evaluating them; and the predictors of symptom outcome and patient satisfaction at 2-week follow-up

TECHNICAL APPROACH

Consecutive patients presenting to a general medicine walk-in clinic with a chief complaint of a physical symptom are eligible and are invitied to fill out a questionnaire regarding symptom characteristics and their own concerns and expectations regarding evaluation and treatment. After the encounter, physicians also filled out a questionnaire. Two weeks later, patients received a follow-up questionnaire in the mail; those not responding were contacted by telephone. Major outcomes anlayzed were prevalence of various patient concerns and expectations, physician recognition of these factors, and symptom outcome and patient satisfaction.

PRIOR AND CURRENT PROGRESS

Pre-visit questionnaires were completed by 328 patients, with corresponding physician questionnaires available for 95%. Patient follow-up questionnaries were completed for 92%. All data has been entered into a data base, and preliminary analysis has been completed. There have been no adverse consequences from this study. Findings have been presented at one scientific meeting and have been submitted to another. Manuscript preparation will begin soon.

CONCLUSIONS

Patient expectations for medications, tests, and referrals were high: 72%, 68%, and 53%, respectively. Two-thirds of the patients feared a serious illness, and 62% reported functional impairment. Concerns and expectations were frequently unrecognized by physicians, and a serious illness worry and desire for tests and referral were still present in > 20% of patients at 2-week follow-up.

REPORT DATE: 02/11/93 WORK UNIT # 1030

DETAIL SUMMARY SHEET

TITLE: Development of a Primary Care Evaluation of Mental Disorders System (PRIME-MD)

KEYWORDS: psychiatry, depression, psychometrics

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: General Medicine Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To develop a valid psychiatric screening instrument, PRIME-MD, that would allow primary care physicians to efficiently diagnose depressive, anxiety, somatoform, alcohol, and eating disorders in their patients.

TECHNICAL APPROACH

A random sample of patients presenting to primary care clinics at four sites (Walter Reed, New England Medical Center in Boston, University of South Alabama, and Albert Einstein in New York) were invited to fill out a one-page patient questionnaire . For any of the five modules (depression, anxiety, etc.) that were positive, physicians asked structured questions out of a Clinician Evaluation GUide to make DSM-III-R phychiatric diagnoses. Patients also completed validating instruments (Zung Depression and Anxiety Scales, Barsky Somatization Scale, etc.), and a sample was re-interviewed by a mental health professional.

PRIOR AND CURRENT PROGRESS

To date, over 900 patients have been enrolled in the study groupwide, and it is anticipated that by the end of February 1993, the target sample of 1000 patients will have been enrolled. Of these, nearly 400 will have had telephone re-interviews. There have been no adverse consequences. Since this is a cross-sectional study design, patient dropout is not an issue. Patient accrual from WRAMC is complete, with a total of 280 patients enrolled. Data collection for the entire study will be complete by March 1, and a draft of the first manuscript is anticipated by July 1993.

CONCLUSIONS

PRIME-MD is efficient, with the average clinician interview taking less than 10 minutes. Psychiatric disorders were present in > 25% of patients, and many had been previously unrecognized. Physicians reported this often led to new therapy and found the instrument quite useful. Preliminary analysis of the validating forms and telephone interviews indicate that PRIME-MD is a valid instrument as well.

REPORT DATE: 02/11/93 WORK UNIT # 1031

DETAIL SUMMARY SHEET

TITLE: Advance Directives: Implementation into Clinical Practice

KEYWORDS: advance directives, ethics

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC
ASSOCIATES: Landry, Francis CPT MC; Lucas, Christine MPH

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if an interactive educational patient seminar increases the number of advance directives formulated by patients, compared to providing written educational materials alone.

TECHNICAL APPROACH

Consecutive patients presenting to the Internal Medicine Clinic on selected half-days will be invited to fill out a questionnaire regarding advance directives (AD), including whether or not they are interested in finding out more about AD. Those potentially interested will be contacted by phone, and if still interested, they will be randomized to recieve written information in the mail or to attend a special seminar on AD. Patients will be contacted several months after the intervention to determine if any actions were taken regarding AD.

PRIOR AND CURRENT PROGRESS

There were 187 interested patients without AD who were randomized to either the seminar (n = 95; study group) or mailed information (n = 92; conrol group). Follow-up was successful for 91% of the patients. Study patients were more likely than controls to have discussed end-of-life issues with family (p = 0.02), to have found the information provided useful (p = 0.02), and to have completed advance directives (p = 0.04). There were no adverse consequences of this study.

CONCLUSIONS

An interactive seminar, which can be conducted with groups of patients, may be an efficient way of implementing advance directives in clinical practice. Hosptials or clinics could easily set up such classes.

REPORT DATE: 11/15/92 WORK UNIT # 1523-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9111. A Trial of G-CSF vs Placebo During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphatic Leukemia

KEYWORDS: adult acute leukemia G-CSF

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare time to bone marrow recovery, infection incidence, days of hospitalization, and tolerance of non-hematopoietic organs after intensive chemotherapy for acute lymphatic leukemia (ALL) in patients given either granulocyte colony-stimulating factor (G-CSF) or placebo; to determine G-CSF's effect on CR rate and duration and mortality (during neutropenia) during intensive induction and intensification; and to compare doses that can be given to G-SF vs placebo patients.

TECHNICAL APPROACH

Eligible patients will be randomly assigned to receive daily subcutaneous injections of either G-CSF or placebo starting 3 days after initial chemotherapy. Injections will continue until the WBC count is normal. The pharmacist will be the only one who knows what the patients will be receiving. The study will remain blinded until after the first month. After being unblinded, patients who received G-CSF will continue to receive it during the next course of therapy. Those who did not, will not receive any further placebo or G-CSF. Patients will receive a series of five different cancer treatments in sequence; each uses combination chemotherapy, and one involves radiation. Total treatment time is 24 months.

PRIOR AND CURRENT PROGRESS

A total of five patients from WRAMC have been entered in this study since it opened. A total of 64 patients have been entered nationwide. All patients from WRAMC are still receiving treatment. No serious and/or unexpected adverse reactions have been noted. Toxicities have been those which were expected. No deaths have occurred from neutropenic fevers. Those patients who were randomized to receive G-CSF appeared to have shorter durations of neutropenia on the institution's review of data; this may represent a benefit derived for those patients.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 12/02/92 WORK UNIT # 1524-91

DETAIL SUMMARY SHEET

TITLE: A NCI/WRAMC Collaborative Phase I Trial of Suramin in Patients with Advanced Solid Tumors

KEYWORDS: carcinoma, metastatic, suramin

PRINCIPAL INVESTIGATOR: Dawson, Nancy LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the efficacy and toxicity of the investigational agent suramin in metastatic refractory cancer.

TECHNICAL APPROACH
Suramin is administered intravenously by continuous infusion until the desired blood level is achieved. Therapy is then continued for 8 weeks maintaining this blood level, then discontinued for 8 weeks, and then reinitiated as in cycle one. Therapy continues every 8 weeks until complete remission, progressive disease, or unacceptable toxicity.

PRIOR AND CURRENT PROGRESS
This protocol is a collaborative effort with the National Cancer Institute. Total patients accrued = 16; total accrued at WRAMC = 4. No patients at Walter Reed have demonstrated tumor progression at the current dosing level. One patient had atrial fibrillation and an upper intestinal hemorrhage attributed to the hydrocortisone prescribed as part of this study. This patient died secondary to subsequent multi-organ failure following surgery for his gastric hemorrhage.

CONCLUSIONS
Study is ongoing. The accrual goal of 30 patients is expected to be reached within 6 months.

REPORT DATE: 08/19/92 WORK UNIT # 1529-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9132: Combination Chemotherapy Plus G-CSF for Advance Non-Small Cell Lung Cancer

KEYWORDS: chemotherapy, growth factor, lung cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FY: $ 0 Total: $ 0

STUDY OBJECTIVE

To screen two combination chemotherapy regimens, Ifosfamide/mesna/cisplatin/G-CSF and etoposide/cisplatin/G-CSF for significant activity in metastatic non-small cell lung cancer (NSCLC) or in locally advanced NSCLC because of a malignant pleural effusion (activity determined by response frequency); to describe overall and failure-free survival for each regimen; to determine duration of response (complete or partial) or regression; and to evaluate toxicity of these regimens.

TECHNICAL APPROACH

Eligible patients are randomized to receive chemotherapy with either: (1) Ifosfamide, Mesna, and cisplatin; or (2) etoposide and cisplatin. Both treatments involve the administration of G-CSF subcutaneously for 8 days following chemotherapy. All chemotherapy drugs are given intravenously for 3 consecutive days. The course is repeated every 21 days for a maximum of 6 months, unless disease progresses.

PRIOR AND CURRENT PROGRESS

Two patients from WRAMC have been entered in this study; one was assigned to treatment 1, and the other to treatment 2. Both patients experienced grade 3-4 hematologic toxicity despite the G-CSF. The patient randomized to treatment 1 experienced grade 4 gastrointestinal toxicity during the first course that required direction from the study chair. No other significant toxicities were observed. Both patients had initial decreases in the size of their tumors with subsequent progression. Both patients have been removed from the study; one is receiving off-protocol chemotherapy, and the other is being followed with stable disease. No withdrawal of consent occurred. The study closed to patient accrual March 1992.

CONCLUSIONS

Data is being analyzed. No conclusions have been reached.

REPORT DATE: 03/12/93 WORK UNIT # 1530-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9181. A Comparative Study of Two Doses of Megace in Advanced Prostate Cancer

KEYWORDS: metastatic disease, dose comparison, quality of life

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the response rate (complete, as well as partial) of megestrol acetate at a 160 mg daily dose versus a moderately high dose of 640 mg daily in patients with metastatic prostate cancer; to describe overall survival and failure-free survival for each of these treatment groups; to determine the relationship between decrease in prostate specific antigen and objective response; and to assess quality of life issue and symptoms.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of two treatments: standard dose of megace daily or high dose (4 times higher than standard) on a daily basis. All patients will complete a quality of life questionnaire before treatment and every 8 weeks thereafter until the end of treatment. Treatment is continued as long as cancer growth is controlled.

PRIOR AND CURRENT PROGRESS

A total of six patients from WRAMC have been enrolled in this study. Three of those patients were removed from treatment due to deep vein thrombosis. It is not known whether this was disease related or treatment related No other similar reports have been received from other institutions. Of the remaining three patients, two have died of progressive disease and one patient committed suicide. The suicide case was reviewed by the IRB in July 1992. A total of 18 patients have been entered nationwide. The projected accrual is for approximately 144 patients.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 12/14/92 WORK UNIT # 1650-87

DETAIL SUMMARY SHEET

TITLE: Exploratory Dose Finding Study to Assess the Efficacy and Safety of Intravenous AHR 11190B (Zacopride Hydrochloride) in the Prevention of Cisplatin-Induced Emesis

KEYWORDS: Zacopride Hydrochloride, IND, drug

PRINCIPAL INVESTIGATOR: Lombardo, Fredric MAJ MS
ASSOCIATES: Adams, Jonathan DCR PHS; Knight, Robert LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Terminated
APPROVAL DATE: Nov 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the efficacy and safety of single doses of Zacopride Hydrochloride in the prevention of cisplatin-induced emesis, and to investigate the dose-response effect of Zacopride Hydrochloride for prevention of emesis caused by cisplatin.

TECHNICAL APPROACH

Protocol outline methodology. A particular dose of Zacopride is given 30 minutes prior to cisplatin infusion. If patients have six or more emetic episodes, Zacopride would be considered a filum, and other antiemetics will be administered.

PRIOR AND CURRENT PROGRESS

This research protocol was administratively terminated.

CONCLUSIONS

This research protocol was administratively terminated.

REPORT DATE: 07/21/93 WORK UNIT # 1658-88

DETAIL SUMMARY SHEET

TITLE: Verification of the Heterogeneity of Lupus Anticoagulant Using Purified IgG and IgM from Patients with Lupus Anticoagulant

KEYWORDS: lupus anticoagulant, cardiolipin antibody

PRINCIPAL INVESTIGATOR: Alving, Barbara LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To obtain blood from patients who have a lupus anticoagulant for the purpose of purifying and characterizing the antiphospholipid activity as being in the IgG or IgM fraction.

TECHNICAL APPROACH
IgG and IgM will be purified by column chromatography using DEAE cellulose from patient plasma.

PRIOR AND CURRENT PROGRESS
A total of 18 patients were enrolled. None were studied during the last year. There have been no adverse reactions to the blood drawing. Immunoglobulins will be purified from the plasmas that have been obtained, and further studies will be done on the interaction of the immunoglobulins with beta2-glycoprotein. It is currently believed that this latter protein is a co-factor for the interaction between immunoglobulins and phospholipids.

CONCLUSIONS
Antibodies demonstrate marked heterogeneity toward ph- -holipids. Multiple plasmas need to be studied to define the range of the heterogeneity.

REPORT DATE: 08/17/93 WORK UNIT # 1668-89

DETAIL SUMMARY SHEET

TITLE: WRAMC 8904: High Dose Chemotherapy and Autologous Bone Marrow Transplantation for Poor Prognosis Lymphomas, Phase II

KEYWORDS: autologous, bone marrow, chemotherapy

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) To test the feasibility of autologous bone marrow harvesting after initial tumor debulking with induction chemotherapy. 2) To determine the toxicity, time to marrow reconstitution, response rate, and time to treatment failure after high dose 3-drug consolidation with autologous bone marrow transplantation (ABMT) support.

TECHNICAL APPROACH

Eligible patients with relapsed lymphomas undergo conventional-dose salvage induction therapy. Those who achieve a response can undergo autologous bone marrow harvesting; followed by consolidation high-dose 3-drug chemotherapy using cyclophosphamide, etoposide, and BCNU; followed by infusion of the autologous bone marrow, which had been cryopreserved after harvesting. The patients are hospitalized until marrow engraftment.

PRIOR AND CURRENT PROGRESS

A total of 14 lymphoma patients have been treated with ABMT at WRAMC; 6 during the past year. Four patients were treated with a 4-drug regimen, with two toxic deaths reported. Other institutions found similar toxicities with this regimen. One patient relapsed and died of lymphoma, and one patient still remains in remission. Ten patients have been treated with a modified regimen, which eliminated the ARA-C and decreased the BCNU to 600 mg; this was tolerated well, without major toxicities. Seven patients are in remission to date, and one relapsed. There was one death related to infection, and one late death post-transplant related to unknown etiology. Two patients have been harvested and will be transplanted after September 1993.

CONCLUSIONS

In conclusion, using the 3-drug regimen with decreased BCNU caused no major toxicities in 10 patients completed to date. Of the 10 patients completed, 6 who have been treated on the 3-drug regimen remain in remission with short-term follow-up. One patient from the 4-drug regimen has a 3 year remission to date.

REPORT DATE: 09/13/93 WORK UNIT # 1669-89

DETAIL SUMMARY SHEET

TITLE: WRAMC 8905: Chemotherapy with Autologous Bone Marrow Support for Selected Advanced Solid Tumors, Phase II

KEYWORDS: bone marrow, chemotherapy, autologous

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the toxicity, time to marrow reconstitution, response rate, and time to treatment failure for high-dose carboplatin, etoposide, and cyclophosphamide therapy with autologous bone marrow support for selected advanced solid tumors.

TECHNICAL APPROACH
Patients selected per eligibility requirements and presentation to Bone Marrow Transplant Conference. Patients undergo autologous bone marrow harvest with marrow separation and cryopreservation. They then receive 6 days of high-dose chemotherapy, followed by infusion of thawed autologous marrow. They are supported until marrow recovery in-hospital. At 60 days after transplant, they undergo reevaluation to assess response to the therapy and are then followed for clinical progression and/or late complications. An amendment was approved by the HUC/IRB in February 1992 to administer cyclophosphamide on the seventh as well as the sixth day of therapy.

PRIOR AND CURRENT PROGRESS
Altogether, 27 patients (20 with breast cancer, 5 with testicular carcinoma, 1 with sarcoma, and 1 with lung cancer) have been treated with high dose chemotherapy and autologous bone marrow support for solid tumors. During the past year nine patients (eight with metastatic breast cancer, and one with refractory testicular cancer) have been treated. Altogether, there have been eight patients in complete remission, six in partial remission, six with stable disease, three with progressive disease, and four deaths. All patients have completed the 60+ day evaluation.

CONCLUSIONS
Chemotherapy with autologous bone marrow support has been well tolerated in patients with selected advanced solid tumors.

REPORT DATE: 05/17/93 WORK UNIT # 1672

DETAIL SUMMARY SHEET

TITLE: 5-Fluorouracil and Low Dose Leucovorin After Ultrasound Guided Laser Ablation of Colorectal Carcinoma Metastatic to the Liver

KEYWORDS: 5-fluorouracil, leucovorin, liver

PRINCIPAL INVESTIGATOR: Ward, Frank LTC MC
ASSOCIATES: Dawson, Nancy LTC MC; Dachman, Abraham MD

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the effectiveness of 5-fluorouracil and low-dose leucovorin as therapy for metastatic colorectal carcinoma to the liver after laser ablation of the hepatic metastases, when compared to historical controls. Primary endpoint is survival. Disease-free interval, progression-free interval, and palliative effect of chemotherapy in conjunction with laser ablation are secondary endpoints.

TECHNICAL APPROACH

Patients who have undergone laser ablation of metastatic colorectal carcinoma to the liver will receive leucovorin (20 mg/m2/d) immediately followed by 5-fluorouracil (425 mg/m2/d) by rapid intravenous injection for 5 consecutive days. Courses will be repeated at 4 weeks, 8 weeks, and every 5 weeks thereafter in the absence of progressive disease or unacceptable toxicity. Survival will be calculated from the date of study entry. Doses will be modified for toxicity.

PRIOR AND CURRENT PROGRESS

This study was opened 3 years ago with no patients accrued to date. This primarily reflects the poor accrual to the hepatic laser ablation protocol.

CONCLUSIONS

Since the principal investigator of the hepatic laser ablation protocol will be leaving this institution and the continuation of that study (the source of patients for this 5-fluorouracil and low dose leucovorin study) is in doubt, this study should be closed.

REPORT DATE: 06/16/93 WORK UNIT # 1675

DETAIL SUMMARY SHEET

TITLE: WRAMC 9004 A Study of Interferon Alpha-2A in Combination with 5FU Plus Leucovorin in Metastatic or Recurrent Colorectal Cancer

KEYWORDS: colorectal cancer, interferon, 5FU/leucovorin

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test the efficacy of the 3-drug regimen in 30 previously untreated metastatic or recurrent colorectal cancer patients.

TECHNICAL APPROACH
Non-randomized study in which all patients receive subcutaneous injections of interferon alpha, high dose IV leucovorin, and standard IV doses of 5FU every 3 weeks.

PRIOR AND CURRENT PROGRESS
A total of eight patients from WRAMC have been entered on this study. No patients were entered during this reporting period. All eight patients have been removed from study due to progressive disease; five patients have died of their disease, the other three are receiving other therapies. No unexpected toxicities were observed, and no patients withdrew consent during treatment. The study closed for new accrual July 1992. The study can now be closed at WRAMC since all patients have been removed from therapy.

CONCLUSIONS
None. Analysis is ongoing.

REPORT DATE: 09/14/93 WORK UNIT #: 1676

DETAIL SUMMARY SHEET

TITLE: Detection of Lupus Anticoagulants in Patients with Anticardiolipin Antibodies

KEYWORDS: lupus anticoagulant, cardiolipin antibody

PRINCIPAL INVESTIGATOR: Alving, Barbara COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if patients with low, medium, or high anticardiolipin antibody titers also have a lupus anticoagulant as determined by two different phospholipid dilution assays.

TECHNICAL APPROACH
Plasma will be obtained from patients known to have anticardiolipin antibodies as determined in the Rheumatology Clinic at WRAMC under the direction of Dr. Joe Tesar. The APTT will be measured in the Coagulation Lab at WRAIR, and tests for lupus anticoagulants will be done utilizing the dilute phospholipid APTT or the RVVT.

PRIOR AND CURRENT PROGRESS
There has been no progress on this project during the past 2 years; however, attempts will be made for one more year to enroll patients. Three patients have been enrolled since the study's inception. The topic is of importance since clinical interest in patients with the antiphospholipid syndrome continues to grow, and appropriate lab testing has not yet been well defined. There have been no adverse reactions from the blood drawing, nor is there any direct benefit to the patients other than they will also have a profile of their coagulation status in addition to the rheumatologic studies.

CONCLUSIONS
Important findings anticipated include ascertaining the best methods for recognition of patients with the antiphospholipid syndrome and determining how well the coagulation assays and solid phase assays for the detection of antiphospholipid antibodies correlate.

REPORT DATE: 04/15/93 WORK UNIT # 1677

DETAIL SUMMARY SHEET

TITLE: Fludarabine Phosphate (FAMP: NSC-312887) in Compassionate Circumstances

KEYWORDS: Fludarabine Phosphate, lymphocytic leukemia, progressive adenopathy

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the effectiveness and side effects of Fludarabine Phosphate (FAMP) in a patient with progressive adenopathy from chronic lymphocytic leukemia.

TECHNICAL APPROACH
This is a National Cancer Institute Group C protocol to provide FAMP to physicians in the management of patients with advanced, refractory chronic lymphocytic leukemia who are not candidates for entry onto ongoing clinical trials; and to determine the response rate, response duration, and toxicity of this regimen.

PRIOR AND CURRENT PROGRESS
The one patient enrolled had a good partial response to the therapy. The patient had the last dose in March 1992 and has been followed closely with CT scans and CBC. There has been evidence of progression, with a CT scan of the abdomen showing increase in the mesenteric adenopathy from the best response. The patient will resume the therapeutic drug if the disease continues to progress or causes symptoms.

CONCLUSIONS
This agent was effective in decreasing tumor burden and will probably provide additional benefit when needed. Since the patient was enrolled in the group C protocol, the Fludarabine will be provided at no cost.

REPORT DATE: 08/24/92 WORK UNIT # 1679

DETAIL SUMMARY SHEET

TITLE: Fludarabine Phosphate (FAMP; NSC-312887) in Compassionate Circumstances

KEYWORDS: Fludarabine

PRINCIPAL INVESTIGATOR: Ward, Frank LTC MC
ASSOCIATES: Lombardo, Frederic MAJ MS

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the effectiveness and side effects of Fludarabine Phosphate (FAMP) when used by a single patient on a compassionate exemption.

TECHNICAL APPROACH
Fludarabine 25 mg/m2/d is given intravenously for 5 days as an IV piggy-back. Repeat therapy is given every 3 weeks.

PRIOR AND CURRENT PROGRESS
One patient was enrolled in this study. Patient had at least a partial response documented after three cycles, with reduction in size of an enlarged left tonsil and marked decrease in the extent of bone marrow involvement by malignant cells. The patient was admitted after his third cycle with mental status changes attributable to Fludarabine, at least in part, and with Pneumocystis carinii pneumonia, reflective of immune compromise related to his treatment. He died of sepsis. His demise is attributable to his underlying disease and the complications attendant to its treatment. This was not a toxic death from Fludarabine. Febrile neutropenia complicated the first cycle of therapy. Since the patient expired, this is the final report on this study. The drug is not investigational.

CONCLUSIONS
FAMP showed some activity in this patient. At autopsy, no evidence of chronic lymphocytic leukemia could be found, but a complete response could not be confirmed since a bone marrow aspirate was not available for study. The drug has the attendant side effects of immune depression and neurotoxicity. These side effects have been described by other physicians who have used this agent.

REPORT DATE: 11/16/92 WORK UNIT # 1680

DETAIL SUMMARY SHEET

TITLE: Anagrelide (IND CA #700-999-422) in Compassionate Circumstances

KEYWORDS: thrombocythemia

PRINCIPAL INVESTIGATOR: Ward, Frank LTC MC
ASSOCIATES: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the effectiveness and side effects of Anagrelide in patients suffering from thrombocythemia of various etiologies.

TECHNICAL APPROACH
Anagrelide at .5 mg by mouth four times a day will be used for the first week. The dose will then be adjusted to control the platelet count. For rapid platelet count reduction, 1 mg by mouth four times a day can be used initially. Platelet counts will be closely monitored to assure thrombocytopenia does not occur. Anagrelide will be given as long as necessary to control platelet counts.

PRIOR AND CURRENT PROGRESS
Two patients are currently enrolled in study. Their platelet counts have been controlled without drug-related toxicity. No patients have withdrawn from the study. These two patients have benefited by the drug's ability to control their platelet counts. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Anagrelide has controlled the platelet counts in these two patients with thrombocythemia without toxicity to date.

REPORT DATE: 04/27/93 WORK UNIT # 1681

DETAIL SUMMARY SHEET

TITLE: Characterization of Human Autoantibodies to Neutrophils and to Bone Marrow Myeloid Precursor Cells

KEYWORDS: neutropenia, autoimmunity

PRINCIPAL INVESTIGATOR: Hartman, Kip LTC MC
ASSOCIATES: Ward, Frank LTC MC; Klipple, Gary COL MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 916 Previous FYs: $ 2,705 Total: $ 3,621

STUDY OBJECTIVE

To characterize the antigenic targets that appear to be involved in the pathogenesis of autoimmune neutropenia.

TECHNICAL APPROACH

This study involves the collection of blood specimens from patients and control subjects. Laboratory evaluation includes flow cytometric measurement of anti-neutrophil antibodies, evaluation of antigenic target proteins using immunoblot and immunoprecipitation techniques, and suppression studies of the growth of myeloid progenitor cells in vitro.

PRIOR AND CURRENT PROGRESS

There have been no adverse reactions to phlebotomy, and there has been no clinical benefit to patients. During the first year of the study, three control subjects and one patient have been registered.

CONCLUSIONS

Autoantibodies to antigens present on myeloid precursor cells may be present in the sera of patients with apparent autoimmune neutropenia. Characterization of the molecular target antigens of these antibodies and their role in the pathogenesis of disease is the subject of ongoing studies.

REPORT DATE: 10/30/92 WORK UNIT # 9022-83

DETAIL SUMMARY SHEET

TITLE. Studies of the Proliferation and Differentiation of Pluripotent Stem Cells and Committed Hematopoietic Precursors from Normal Bone Marrow Maintained in Continuous Long-term Cultures

KEYWORDS: stem cells, differentiation

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC
ASSOCIATES: La Russa, Vincent PhD; Salvado, August COL MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1982

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define mechanisms by which progenitor cells in the bone marrow replicate themselves and go on to form mature blood cells.

TECHNICAL APPROACH
The methods involved are: 1) the use of culture tubes and a defined media to study the behavior of stem cells for a period up to 8 weeks in culture; and 2) the use of clonal assays to quantitate the number of stem cells grown in culture.

PRIOR AND CURRENT PROGRESS
To date, 724 bone marrow specimens have been collected for this study; 52 during the past year. The pathophysiology of dengue virus infection on bone marrow cells and the use of the long-term marrow culture system as a predictor of virus attenuation for man for screening candidate live virus vaccines continue to be studied. Additionally, this work has shown that primitive hematopoietic cells responsible for long-term engraftment can be enriched by treating purified CD34+ cells with a novel immunotoxin, anti-CD33 blocked-ricin immunotoxin, which has also been shown to kill AML cells. This drug is now currently used in clinical trials. Lastly, serum deprived cultures have been used to study the physiology of immature hematopoietic cells from the bone marrow. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
The results from these studies will elucidate on mechanisms involved in the regulation of hematopoiesis in the normal and disease-state.

REPORT DATE: 07/16/93 WORK UNIT # 1956

DETAIL SUMMARY SHEET

TITLE: Neutrophil Function in Patients with Diabetes Mellitus

KEYWORDS: diabetes mellitus, neutrophil, myeloperoxidase

PRINCIPAL INVESTIGATOR: Cross, Alan COL MC
ASSOCIATES: Glass, Allan COL MC; Duncan, William LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Completed
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 7,236 Total: $ 7,236

STUDY OBJECTIVE

To assess 1) neutrophil function of patients with diabetes mellitus and determine if impaired functional responses of diabetic neutrophils are related to a defect in the incorporation of exogenous inositol into hormonally sensitive phosphatidyl inositol pools, 2) lymphocyte function in diabetics by measuring expression of IL2 receptors, HLA-DR antigens, and IL2 production, and 3) neutrophil function by measuring calcium levels, and membrane depolarization.

TECHNICAL APPROACH

Since submitting an amendment to this protocol in 1988, the most significant finding has been that the initial rates of superoxide formation in diabetics is twice that of controls; however, 10 minutes after stimulation, the neutrophils of diabetic patients generate levels of superoxide that are 25% that of controls. Resting, but not stimulated, intracellular calcium levels also differed between the two groups. The expression of IL2 receptors in response to some stimuli differed between the two groups. We are now correlating these differences with clinical parameters.

PRIOR AND CURRENT PROGRESS

Since July 1991, no further subjects have been entered into the study. A total of 40 patients and 26 controls were enrolled since this study's approval. There have been no serious or unexpected adverse reactions, and no patient has withdrawn from the study. Analysis of the patients to date reveals no gross differences in MPO activity between patients with types I and II diabetes. There has been no clear benefit to patients entered in this study. Work will continue at WRAIR with neutrophils from healthy donors in which controlled amounts of glucose and myoinositol will be added to assess these effects on MPO activity.

CONCLUSIONS

Despite clear evidence of a susceptibility to infection among patients with diabetes, no clear defect in neutrophil function has been documented in this study or by others.

REPORT DATE: 02/18/93 WORK UNIT # 1965

DETAIL SUMMARY SHEET

TITLE: Treatment of Cutaneous Leishmaniasis with Pentostam

KEYWORDS: leishmaniasis, Pentostam, IND

PRINCIPAL INVESTIGATOR: Johnson, Steven MAJ MC
ASSOCIATES: Magill, Alan MAJ MC; Gasser, Robert Jr. LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) Provide continuous therapy for cutaneous leishmaniasis; 2) Determine peak and trough serum concentrations, and serum half-life, of Pentostam administered at a dose of 20 mg antimony (Sb)/kg body weight daily for 20 days; 3) Collect additional safety data on this dosing regimen; and 4) Compare 10 days therapy with 20 mg Sb/kg/day to 20 days therapy with 20 mg Sb/kg/day.

TECHNICAL APPROACH

Administration of Pentostam to patients diagnosed as having cutaneous leishmaniasis. Approximately five patients meeting the criteria for receiving Pentostam will be asked to donate blood in order to study the pharmacokinetics of this drug. This protocol will also provide for the randomization of patients to two groups: Group A will receive 20 mg Sb/kg/day for 20 days, and Group B will receive 20 mg Sb/kg/day for 10 days, followed by 50 ml DSW IV qd for 10 additional days. A total of 40 patients will be randomized. Five from each group will be asked to participate in the pharmacokinetic study.

PRIOR AND CURRENT PROGRESS

During 1992, nine patients with cutaneous or mucocutaneous leishmaniasis participated; for a total of 150. Treatment was followed by improvement or resolution of skin lesions in seven, and persistence of lesions in two. Pancreatistis was newly identified as a frequent complication of therapy with Pentostam. Due to pancreatitis, therapy was interrupted in two patients who later completed the planned regimen and was stopped in two others. Pentostam was briefly interrupted in one other patients due to transaminase elevations. One patient whose skin lesions failed to respond to initial treatment with Pentostam was retreated, but retreatment was stopped due to severe musculoskeletal pains.

CONCLUSIONS

In most cases at Walter Reed, Pentostam therapy has been associated with clearing of cutaneous lesions from leishmaniasis, but the drug induces adverse effects with high frequency.

REPORT DATE: 07/15/93 WORK UNIT # 1967

DETAIL SUMMARY SHEET

TITLE: Pharmacokinetics of Polyvalent Hyperimmune Globuin Directed Against Pseudomonas and Klebsiella

KEYWORDS: immunoglobulin, Pseudomonas, Klebsiella

PRINCIPAL INVESTIGATOR: Cross, Alan COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Infectious Disease Service APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the pharmacokinetics of IVIG directed against gram negative germs in patients who are ill and in normal volunteers.

TECHNICAL APPROACH
Volunteers will be given immunoglobulin and have their blood drawn at specified periods of time. The ELISA results will be subjected to pharmacokinetic analysis. In an addendum approved during FY93, a follow-up study will utilize ELISpot assay of lymphocytes and the measurement of serum IgG, IgA, and IgM against specific bacterial antigens to assess if passively administered IVIG induces new specific antibody formation.

PRIOR AND CURRENT PROGRESS
Initial studies performed as part of this protocol suggested that new antibody was being formed in response to the passive infusion of immunoglobulin hyperimmune to Klebsiella and Pseudomonas antigens. To test this hypothesis directly, approval was received in March 1993 to infuse both standard and hyperimmune immunoglobulin to normal volunteers and measure their antibody response to specific bacterial antigens. The infusions were performed without incident on two volunteers last week. New antibody formation is being monitored. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Passive administration of specific antigens may also actively immunize against those specific antigens, perhaps through the idiotypic network. If true, passive administration of hyperimmune immunoglobulins may provide long-lived protection to patients at risk.

REPORT DATE: 11/17/92 WORK UNIT # 1974

DETAIL SUMMARY SHEET

TITLE: Phase I Trial of a Polyvalent Escherichia Coli-Toxin A Conjugate Vaccine

KEYWORDS: E. coli, vaccine, polysaccharide

PRINCIPAL INVESTIGATOR: Artenstein, Andrew MAJ MC
ASSOCIATES: Cross, Alan COL MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether a polyvalent E. coli O-polysaccharide-toxin A conjugate vaccine is safe and immunogenic when administered to humans.

TECHNICAL APPROACH

This is a Phase I study of a polyvalent polysaccharide vaccine against common bacteremic strains of E. coli. A group of healthy volunteers will be injected with this product, and serial serum chemistries, side effect diaries, and various antibody measurements will be assessed on each subject.

PRIOR AND CURRENT PROGRESS

The study has been completed and is closed, except for ongoing antibody measurements and functional assays of vaccinated individuals' serum. Fourteen healthy volunteers were immunized with the polyvalent vaccine in this protocol (all during the first year of the study). No serious or unexpected adverse reactions were noted, and no one was taken off study. Most volunteers reported local pain or tenderness at the site for up to 48 hours. There were no significant changes over baseline in serum chemistries in the vaccinated individuals. Immunologic responses to O-polysaccharides are in the process of analysis, but they appear to depend on pre-immunization antibody levels, with the greatest changes in those with the lowest baselines.

CONCLUSIONS

The polyvalent E. coli O-polysaccharide vaccine is safe when administered to healthy volunteers, and it may be possible to induce functionally active antibody in these individuals.

REPORT DATE: 11/29/92 WORK UNIT # 1157

DETAIL SUMMARY SHEET

TITLE: Effects of Thyroid Hormone and Thyrotropin (TSH) on Cultured Kidney Cells: Modulation of ANP Receptors and Epithelial Function

KEYWORDS: ANP, thyroid hormone, kidney

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Tseng, Yueh-Chu PhD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 7,796 Total: $ 7,796

STUDY OBJECTIVE

To determine whether the number or binding affinity of ANP receptors on renal cells is affected by incubation of such cells with ranging concentrations of thyroid hormone and thyroid hormone-depleted media; to correlate any changes with post-receptor and functional events.

TECHNICAL APPROACH

Rat papillary collecting duct cells (PCDC) were obtained as a gift from Dr. John Schwartz, Boston University. The ANP receptor in these cells will be indentified and characterized under control conditions, and in cells grown in T3-free media and media enriched with T3. The ANP receptor will be characterized using hot and cold ANP. Guanylate cyclose (cyclic GMP) will be measured using kit.

PRIOR AND CURRENT PROGRESS

PCDC exhibited very low specific binding at 37 C and 25 C. At 4 C, a receptor Kd of 11nM and 1,500,000 binding sites/cell were identified. When cells were grown in T3-free media, or media enriched with T3, no change in specific binding was noted. ANP did produce significant changes in cyclic GMP, but T-3 did not affect cyclic GMP levels.

CONCLUSIONS

Any thyroidal influence on the renal cellular response to ANP is not mediated by changes in the number of receptors or binding affinity of such receptors in the PCDC model. A manuscript is in preparation.

REPORT DATE: 11/18/92 WORK UNIT # 1161

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Action of Thiorphan and Atrial Natriuretic Peptide on Renal Function During Hemorrhagic Shock

KEYWORDS: kidney, shock, ANP

PRINCIPAL INVESTIGATOR: Yuan, Christine CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 709 Previous FYs: $ 3,530 Total: $ 4,239

STUDY OBJECTIVE

To study the effects of atrial natriuretic peptide (ANP) and Thiorphan in renal function during hemorrhagic shock in the rat model. The researchers have previously found that renal function and urine output are acutely improved by this drug, and now wish to study whether renal blood flow is changed by the regimen and whether renal function also is affected 48 hours after hemorrhage.

TECHNICAL APPROACH

Renal artery blood flow will be measured during hemorrhage in animals receiving Thiorphan, ANP, both, or vehicle. In addition, chronic survival studies of GFR, UO, solute excretion, and renal histology are underway. This involves exposing the animal to sublethal hemorrhage while administering ANP/Thiorphan or vehicle, and then measuring UO, Na excretion, and inulin clearance 24 hours later.

PRIOR AND CURRENT PROGRESS

Chronic survival experiments are nearly completed. Twenty animals have been used this year (for a total of 27), and 10 more will be required. Animals survive surgery and hemorrhage about 75% of the time, and appear to have a polyuric form of renal injury. Renal blood flow studies are complete.

CONCLUSIONS

No further conclusions can be drawn until the chronic studies are complete.

REPORT DATE: 01/07/93 WORK UNIT # 1162

DETAIL SUMMARY SHEET

TITLE: The Regulation of Insulin-like Growth Factor I and Insulin-like Growth Factor Binding Protein Gene Expression in the Mouse Glomerulus

KEYWORDS: TIMP-1, gelatinase, glomerulosclerosis

PRINCIPAL INVESTIGATOR: Carome, Michael CPT MC
ASSOCIATES: Moore, Jack COL MC; Striker, Liliane MD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 5,043 Previous FYs: $ 8,598 Total: $ 13,641

STUDY OBJECTIVE

To elucidate the molecular and cellular biologic events which lead to the development of glomerulosclerosis. In particular, we are studying the effects of the growth hormone (GH)-IGF-I axis on the gene expression of extracellular matrix (ECM) components, matrix metalloproteinases (MMP), and tissue inhibitor of metalloproteinase (TIMP).

TECHNICAL APPROACH

Matrix synthesis and degradation display will be displayed in vitro in mesangial cells derived from normal and bGH transgenic mice, and in vivo in glomeruli isolated by microdissection from these same animals. The bGH mice will provide a murine model for non-proliferative glomerulosclerosis. Gene expression of ECM, MMP's, and TIMP will be assessed at the mRNA level by in situ reverse transcription, followed by competitive PCR quantitation of the cDNA's of interest. Gelatinase secretion, TIMP-1 synthesis, and collagen secretion will be measured by standard techniques. Renal histology will be assessed by light and immunofluorescence microscopy.

PRIOR AND CURRENT PROGRESS

The study demonstrated that cultured mesangial cells derived from both normal mice and from mice transgenic for bGH, synthesize and secrete TIMP-1 and 72 kDa gelatinase. Only the normal mesangial cells secrete significant amounts of 72 kDa gelatinase. The study also demonstrated that normal murine glomeruli express in vivo 72 kDa gelatinase mRNA and protein, and the expression level is significantly increased in glomeruli of the bGH mice. This increase was not due to an increased glomerular cell number, based upon morphometric analysis. In contrast to the in vitro findings in cultured mesangial cells, TIMP-1 gene expression was not detectable in glomeruli from normal or bGH mice. During the past year, 17 mice were used (8bGH/9 normal). To date, a total of 26 animals have been studied. No unexpected adverse reactions or findings have occurred.

CONCLUSIONS

There were significant differences in the expression of gelatinase and TIMP-1 between intact glomeruli and mesangial cells in vitro, and an up regulation in the expression of 72 kDa gelatinase in bGH glomeruli as compared to normal controls. Elucidation of the mechanisms underlying these differences may enhance the understanding of glomerulosclerosis, and the role of the GH-IGF-I axis in this disease process.

REPORT DATE: 03/12/93 WORK UNIT # 1163

DETAIL SUMMARY SHEET

TITLE: Effects of Cyclosporin A on the Production of Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: cyclosporin A, endothelin, prostacyclin

PRINCIPAL INVESTIGATOR: Yuan, Christine CPT MC
ASSOCIATES: Kiandoli, Luana BSc(MT); Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 3,485 Total: $ 3,485

STUDY OBJECTIVE

To determine whether cyclosporin A can directly stimulate endothelin release from cultured endothelial cells; and if so, is the release of other endothelial-derived vasoactive substances perturbed.

TECHNICAL APPROACH

Both human and bovine endothelial cells in culture will be exposed to varying concentrations of cyclosporine. Endothelin and prostacyclin production will be measured at 24 hours, and cell viability will be assessed at 24 hours. Phosphoramidon, an inhibitor of endothelin release, was added also, and the effect on endothelin and prostacyclin production was measured.

PRIOR AND CURRENT PROGRESS

Cyclosporine stimulated endothelin production in a dose-dependent manner and also stimulated prostacyclin production. Cell viability declines in a dose-deperdent manner. Phosphoramidon inhibited both endothelin and prostacyclin production, but not the decline in cell viability. The response of both intracellular and released big endothelin particles to both cyclosporine and to cyclosporine and Phosphoramidon is being measured. A paper is being prepared.

CONCLUSIONS

Cyclosporine stimulates endothelin and prostacyclin production in a dose dependent manner. Phosphoramidon inhibits production of both hormones but has no effect on the decline in cell viability produced by increasing concentrations of cyclosporine.

REPORT DATE: 04/15/93 WORK UNIT # 1164

DETAIL SUMMARY SHEET

TITLE: Synthesis and Degradation of Collagen and Modulation of its Biology in Sclerosing Forms of Human Glomerulonephritis: Analysis of Gene Expression

KEYWORDS: glomerulonephritis, collagen, TIMP

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Carome, Michael MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $18,944 Previous FYs: $ 16,810 Total: $ 35,754

STUDY OBJECTIVE

To obtain isolated golmeruli from patients with glomerulonephritis (GN) or patients who are undergoing nephrectomy for renal cancer. To use these glomeruli to explore the balance between collagen synthesis and degradation by (a) analyzing the synthesis of Type I and IV collagen, and (b) analyzing the biodegradation of collagen by measuring the synthesis of tissue inhibitor of metalloproteinase (TIMP) 1 and 2.

TECHNICAL APPROACH

Tissue from patients with GN or normal tissue removed from cancer nephrectomies are microdissected to obtain isolated glomeruli. The glomeruli are solubilized with triton, and messenger RNA (mRNA) is inhibited. Messenger RNA is reverse transcribed into stable cDNA. Then this cDNA is used, with appropriate primers, in a competitive PCR experiment which allows detection of mRNA for both TIMP's. Mutant TIMP's are constructed and run in the competitive PCR, and the mutant product is compared to wild type. This allows quantitation of the different forms of TIMP. Light microscopic analysis of tissue is performed.

PRIOR AND CURRENT PROGRESS

Five new subjects were studied in the last year, for a total of 15. There have been no serious and/or unexpected adverse reactions. Using tissue taken from nephrectomy patients, this study demonstrated that normal human glomeruli expressed in vivo the genes for the a2, a3, and a5 Type IV collagen chains, TIMP-1, TIMP-2, and 72 kDa gelatinase; and that the level of expression for Type IV collagen and the TIMP's was significantly increased in glomerulosclerosis associated with renal cell carcinoma. TIMP-2 protein was found within the mesangium by immunofluorescence microscropy. The study also demonstrated that the technique of RT-PCR can detect and quantitate mRNA levels in glomeruli of patients undergoing clinical percutaneous renal biopsies.

CONCLUSIONS

Normal glomeruli expressed Type IV collagen, TIMP-1, TIMP-2, and gelatinase mRNA in vivo. Increased expression of Type IV collagen and TIMP's may contribute to the development of some forms of glomerulosclerosis. Application of study techniques to clinical biopsy specimens may enhance understanding of molecular events involved in development of glomerulosclerosis.

REPORT DATE: 09/07/93 WORK UNIT # 1165

DETAIL SUMMARY SHEET

TITLE: The Effects of Cisplatin on the Production of Endothelin and Other Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: cisplatin, endothelin, prostacyclin

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 4,868 Previous FYs: $ 2,587 Total: $ 7,455

STUDY OBJECTIVE

To determine whether cisplatin can directly stimulate endothelin release from cultured endothelial cells; and if so, is the release of other endothelial derived vasoactive substances perturbed.

TECHNICAL APPROACH

Endothelial cells in culture will be exposed to varying concentrations of cisplatin. Cell viability will be assessed at 24 hours. Endothelin and prostacyclin production will be measured at 24 hours. The endothelial cells used in this study will be purchased off-shelf.

PRIOR AND CURRENT PROGRESS

Human umbilical vein endothelial cells (HUVEC) between passage 14 and 16 were grown in F12 media 100,000 cells/well for 24 hours and then exposed to cisplatin (10-1000 ng/ml) for 4, 8, or 24 hours. Control cells were treated with similar dilutions of vehicle. The supernatant was removed for measurement of endothelin and 6-keto-prostaglandin-F1-alpha. Endothelin secretion was not significantly increased by cisplatin as compared to controls at any time. Prostacyclin production was not stimulated in cisplatin treated cells as compared to controls at 24 hours.

CONCLUSIONS

These data suggest that the toxicity of cisplatin is not mediated through endothelin and/or prostanoid production by the vasculature. A combination of insults (i.e., hypoxia and nephrotoxin) may be necessary and would be worth studying in the future.

REPORT DATE: 11/19/92 WORK UNIT # 1166

DETAIL SUMMARY SHEET

TITLE: The Effects of Gentamicin on the Production of Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: endothelin, gentamicin, prostacyclin

PRINCIPAL INVESTIGATOR: Yuan, Christine CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 7,527 Previous FYs: $ 4,582 Total: $ 12,109

STUDY OBJECTIVE
To determine if gentamicin (1) can directly stimulate cultured endothelial cells to secrete endothelin, and (2) affects the production of other endothelial-derived vasocative substances.

TECHNICAL APPROACH
Endothelial cells in culture will be exposed to gentamicin in a dose response experiment. Viability and supernatant levels of endothelin and prostacyclin levels will be measured at 0, 4, 8, and 24 hours.

PRIOR AND CURRENT PROGRESS
Gentamicin does not appear to stimulate endothelin or prostacyclin production in human umbilical vein endothelium, either in a time or dose-dependent fashion. Findings from this study will be submitted for presentation to the AFCR/ASCI Meeting in May 1993.

CONCLUSIONS
As above.

REPORT DATE: 11/12/92 WORK UNIT # 1167

DETAIL SUMMARY SHEET

TITLE: The Effect of Enalapril on Hypertension, Proteinuria, and Renal Function in a New Model of Diabetes Mellitus in Wistar Rats

KEYWORDS: diabetes, hypertension, enalapril

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC
ASSOCIATES: Yuan, Christine CPT MC; Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 5,434 Previous FYs: $ 4,324 Total: $ 9,758

STUDY OBJECTIVE

To determine whether angiotensin converting enzyme inhibitor (CEI) and Dup753 (angiotensin II receptor blocker), when used in this model of diabetes and hypertension, can eliminate or diminish proteinuria, prevent or attenuate the development of renal failure, control the systemic hypertension, and prevent or attenuate renal structural changes.

TECHNICAL APPROACH

The rat model will be used in this study. All animals will undergo 25% reduction in renal mass/streptozotocin injection to create hypertensive, diabetic rats. Animals will then be randomized to receive: (1) enalapril, (2) DuP753, or (3) tap water for 4, 10, or 16 weeks. Blood pressure (BP), renal clearances, proteinuria, and renal pathology will be determined at the three time points.

PRIOR AND CURRENT PROGRESS

Untreated animals showed increased direct arterial blood pressures at time of euthanasia. Animals treated with enalapril or DuP753 had not developed BP elevations and had significantly lower mean arterial pressures than control animals at the time of euthanasia. At 10 weeks after induction of diabetes, inulin clearance (a measure of glomerular filtration rate) was greater in animals treated with enalapril vs. controls. Preliminary renal histology in 16 week rats shows that they develop changes seen in diabetic nephropathy--mesangial expansion, glomerular sclerosis, and thickening of the glomerular capillary loops. Clearance data, urinary protein excretion, and final renal histology are still outstanding. Ninety rats have been used in the past year. There have not been any serious or unexpected adverse reactions or findings.

CONCLUSIONS

Enalapril and DuP753 have antihypertensive effects in this model. Glomerular filtration rate was higher in enalapril-treated rats as compared to controls at 10 weeks. Complete data analysis is not done at this time.

REPORT DATE: 01/14/93 WORK UNIT # 1168

DETAIL SUMMARY SHEET

TITLE: The Acute Effect of Enalapril on Hypertension in a New Model of Hypertension Associated with Diabetes Mellitus in Wistar Rats

KEYWORDS: hypertension, diabetes, angiotensin II

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC
ASSOCIATES: Yuan, Christine MAJ MC; Pamnani, Moti MD PhD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 5,017 Previous FYs: $ 5,593 Total: $ 10,610

STUDY OBJECTIVE

To determine the acute effects of angiotensin converting enzyme therapy on the hypertension seen in a new model of experimental diabetic nephropathy which results in proteinuria, renal failure, and hypertension.

TECHNICAL APPROACH

Male Wistar rats will undergo 25% reduction in renal mass, and diabetes will be induced with IV streptozotocin. After 4 weeks of diabetes, animals will be anesthetized with Inactin and direct blood pressure measured. Animals will then receive either a) DuP753 (an angiotensin II receptor blocker) followed by enalapril (a converting enzyme inhibitor), b) DuP753 vehicle followed by enalapril, or c) both vehicles. Mean arterial pressure, pulse, and urine output will be measured during these manipulations.

PRIOR AND CURRENT PROGRESS

Thirty-five rats have been entered into the protocol. Enalapril and DuP753 when given acutely produce equivalent decrements in mean arterial pressure. Urinary prostanoid excretion is not influenced by either drug. Urinary kinin excretion data is pending.

CONCLUSIONS

The acute antihypertensive effect of enalapril in this model appears to be due only to inhibition of angiotensin II formation.

REPORT DATE: 02/05/93 WORK UNIT # 1169

DETAIL SUMMARY SHEET

TITLE: Safety and Immunogenicity of Staphylococcus Aureus Capsular Polysaccharide - Pseudomonas Aeruginosa, r-exoprotein A type 5 Conjugate Vaccine Given to Patients with End-Stage Renal Disease (ESRD)

KEYWORDS: Staphylococcus aureus, vaccine, dialysis

PRINCIPAL INVESTIGATOR: Welch, Paul MAJ MC
ASSOCIATES: Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 150 Previous FYs: $ 0 Total: $ 150

STUDY OBJECTIVE

To determine (1) the safety and immunogenicity of Staphylococcus aureus capsular polysaccharide - type 5 conjugate vaccine given to patients on dialysis; (2) if there is a booster response to the second injection of vaccine, given 6 weeks after the first injection; and (3) the nasal carriage rate of Staphylococcus aureus in the patients.

TECHNICAL APPROACH

Patients who meet the inclusion and exclusion criteria will be given the study vaccine, followed 6 weeks later by a booster injection. Safety will be evaluated by monitoring patients' symptoms, temperature, local skin reaction, SGOT, and SGPT. Immunogenicity will be evaluated by measuring the antibody response to the vaccine. Nasal carriage rate will be determined by measuring nasal cultures.

PRIOR AND CURRENT PROGRESS

Seventeen patients have been enrolled in the study and given the vaccine. There have been no severe reactions. Only mild reactions have been described, such as temporary local skin changes which resolved in a few days. Temperature, SGOT, and SGPT's did not change. Preliminary assessment of antibody response in the dialysis patients is similar to antibody response in normal subjects given the vaccine in a prior study. There was no booster response. Five of 17 patients were nasal carriers for S. aureus. Final data collection is scheduled for March 1993. There have been no patient drop-outs, and no obvious benefits to them. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

None at this time.

REPORT DATE: 09/15/93 WORK UNIT # 1170

DETAIL SUMMARY SHEET

TITLE: Stress Proteins and Cytoprotection in MDCK Cells in Culture

KEYWORDS: heat shock, cytoprotection, renal tubular cells

PRINCIPAL INVESTIGATOR: Yuan, Christina MAJ MC
ASSOCIATES: Carome, Michael MAJ MC; Bohen, Erin MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $21,208 Previous FYs: $ 0 Total: $ 21,208

STUDY OBJECTIVE

To study the effects of several renal toxins on heat shock protein production by the MDCK cells, a renal tubular cell line, and to test whether previous heat shock is protective to the MDCK cell when treated with known cellular toxins (such as cyclosporine, indomethacin, or gentamicin).

TECHNICAL APPROACH

MDCK cells will be heat-shocked, exposed to several toxins in increasing doses, and measured for HSP70 protein levels via ELISA. Cell viability will be assessed with increasing doses of toxin in cells heat-shocked 24 hours prior to toxin exposure and in control cells. An addendum was approved in June 1993 to study the effect of blocking HSP70 production on viability of heat-shocked cyclosporine treated MDCK cells.

PRIOR AND CURRENT PROGRESS

When MDCK cells were heat-shocked, HSP70 (a heat-shock protein) was shown to increase. Cells heat-shocked 24 hours prior to exposure to cyclosporine have greater viability than control cells that were not heat-shocked prior to cyclosporine exposure. Treatment with sublethal dose of cyclosporine at the time of heat-shocking does not appear to affect HSP70 production. However, treatment with cyclosporine at sublethal doses for 24 hours prior to heat shock does appear to suppress HSP70 production.

CONCLUSIONS

Heat shock is protective to MDCK cells treated with the toxin, cyclosporine. Pre-treatment of MDCK cells with sublethal doses of cyclosporine may prevent production of HSP70.

REPORT DATE: 02/08/93 WORK UNIT # 3011

DETAIL SUMMARY SHEET

TITLE: Comparison of Work of Breathing During Mechanical Ventilation Using Assist Control and Intermittent Mandatory Ventilation

KEYWORDS: work of breathing, mechanical ventilation, oxygen consumption (VO2)

PRINCIPAL INVESTIGATOR: Poropatich, Ronald MAJ MC
ASSOCIATES: Stoltzfus, Daniel MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary & Critical Care Medicine Servi

STATUS: Ongoing
APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 697 Previous FYs: $ 0 Total: $ 697

STUDY OBJECTIVE

To determine whether the work of breathing is significantly different for patients receiving full ventilatory support with assist control versus intermittent mandatory ventilation.

TECHNICAL APPROACH

The study is a prospective, randomized, double blinded, two-period crossover design. Patients receiving mechanical ventilation will be randomly placed on one of the two modes of ventilation. Their VO2 will be measured by the metabolic cart. They will then be placed on the other mode and again have their VO2 measured. These VO2 values will be compared for the two modes. To ensure that there is no change in VO2 nonrespiratory during the study period, it will be measured at the beginning and end by adjusting the ventilator so that the patient makes no respiratory efforts, thus eliminating any respiratory component of VO2. Assuming these values are consistent, differences will be due to the work of breathing.

PRIOR AND CURRENT PROGRESS

To date, one patient has been enrolled in the study. There have been no adverse effects. No patients enrolled since last year due to technical problems with the metabolic cart.

CONCLUSIONS

It is too premature to comment on any study conclusions. Additional time will be necessary to complete the study.

REPORT DATE: 03/03/93 WORK UNIT # 1707

DETAIL SUMMARY SHEET

TITLE: Relationship Between Respiratory Control Mechanisms and Nocturnal Desaturation in Diffuse Pulmonary Fibrosis

KEYWORDS: fibrosis, sleep, respiratory control

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC
ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 11,787 Total: $ 11,787

STUDY OBJECTIVE

To examine the relationship between respiratory control mechanisms and sleep desaturation in patients with pulmonary fibrosis.

TECHNICAL APPROACH

Patients with well defined diffused pulmonary fibrosis will be included in the study, and their results will be compared to results from similar tests performed in a group of volunteer controls. Nocturnal polysomnography and hypercapnic ventilatory and occlusion pressure (P100) responses will be performed to quantitate respiratory control mechanisms and nocturnal desaturation. The SPSS statistical package will be used for evaluation of correlates and co-correlates.

PRIOR AND CURRENT PROGRESS

This is an important study. Eleven patients have been enrolled and completed, to date; none over the last 18 months. A new lab director has been hired, but most efforts have gone into training the technician. Since this is an old protocol and information in this area is very limited, the plan is to rewrite and resubmit this study to DCI over the next 6 months. In the interim, this protocol remains open for patient accrual.

CONCLUSIONS

Nocturnal hypoxemia can be predicted from age and daytime saturation.

REPORT DATE: 09/30/93 WORK UNIT # 1714

DETAIL SUMMARY SHEET

TITLE: Mechanisms Limiting Exercise Ventilation in Chronic Obstructive Lung Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Sep 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 220 Total: $ 220

STUDY OBJECTIVE

To determine factors that limit ventilation at maximum exercise in patients with chronic obstructive lung disease (COPD).

TECHNICAL APPROACH

Continuous physiologic measurements will be made on a bicycle ergometer during graded resistance exercise, with esophageal balloon in place for the measurement of pleural pressure to determine the work of breathing.

PRIOR AND CURRENT PROGRESS

Thirteen subjects have been enrolled and have completed the protocol. No data collection has been undertaken during the past year. From the standpoint of human use, data collection on this protocol has been completed. The basic problem with this project remains the difficulty in conversion of analog tracings to usable digital data.

CONCLUSIONS

Definitive data analysis remains to be completed. A need for support of data analysis and publication in the future may be expected. A new protocol can be submitted if required to permit continued approaches to data reduction.

REPORT DATE: 05/21/93 WORK UNIT # 1717 ·

DETAIL SUMMARY SHEET

TITLE: Prediction of Maximum Exercise Response from Resting Pulmonary Function in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Hnatiuk, Oleh MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: May 1985

FUNDING: Current FY: $ 1,727 Previous FYs: $ 1,090 Total: $ 2,817

STUDY OBJECTIVE

To test the hypothesis that assessment of inspiratory function in addition to expiratory function can improve the prediction of the exercise response of patients with chronic obstructive pulmonary disease (COPD).

TECHNICAL APPROACH

To evaluate parameters of both inspiratory and expiratory function in COPD patients, and to perform exercise tests in this group. Using these variables, prediction formulae with the highest r2 values will be identified for maximum exercise ventilation and oxygen consumption. Data will be collected through record review.

PRIOR AND CURRENT PROGRESS

Total enrollment to date consists of 105 patients for pulmonary function tests and 30 patients for exercise tests (no subjects were enrolled during the past year). One abstract was presented at the Annual Meeting of the American Thoracic Society in May 1993. This will be submitted for publication as an article. One manuscript was published in the American Review of Respiratory Diseases in April 1993. Activity on this protocol consists of data analysis and reporting of results.

CONCLUSIONS

Data thus far indicate that maximum inspiratory flow rate from resting forced spirometry is a useful second order predictor of maximum ventilation. Maximum inspiratory pressure generated at the mouth is a predictor of maximum oxygen consumption in COPD patients. The need for additional support under this manuscript is anticipated.

REPORT DATE: 01/07/93 WORK UNIT # 1724

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Hypoxia During Simulated Air Travel in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: hypoxia, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Berg, Benjamin MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 220 Previous FYs: $ 5,058 Total: $ 5,278

STUDY OBJECTIVE

To describe the hypoxic response to altitude simulation in COPD patients, to identify determinants, and to compare treatment modalities.

TECHNICAL APPROACH

The methods use hypobaric hypoxia to produce hypoxemia. Determinant variables are measured using pulmonary function tests at ground level and hypobaric hypoxia. Treatment with oxygen by two modes of delivery is evaluated at altitude conditions.

PRIOR AND CURRENT PROGRESS

No complications have been reported to date. Data collection has been completed for 27 subjects. Publication of major findings was accomplished in FY 92. Additional manuscripts have been accepted for publication in FY 93. Data analysis continues and additional manuscripts are planned.

CONCLUSIONS

Protocol should remain open since data analysis and manuscript preparation are ongoing.

REPORT DATE: 03/03/93 WORK UNIT # 1725

DETAIL SUMMARY SHEET

TITLE: Evaluation of Inspiratory Parameters in the Response to Inhaled Bronchodilators

KEYWORDS: inspiration, mechanics, bronchodilators

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the effects of improvement in inspiratory measures on the relief in symptoms following the use of bronchodilator medication in patients with airflow obstruction.

TECHNICAL APPROACH
Pulmonary function tests will be performed before and after the inhalation of bronchodilator medications in patients with airflow obstruction. Inspiratory parameters will be examined, and changes in these parameters will be correlated with changes in subjective symptoms.

PRIOR AND CURRENT PROGRESS
Because the person collecting the data has to physically sit in the PFT lab waiting for patients that meet the eligibility criteria, and generally one or two patients are enrolled every 2 days, patient accrual has been slow. Altogether, 30 patients have been enrolled; 10 during the past year. This study should be closed with the next Annual Progress Report.

CONCLUSIONS
No conclusions to date.

REPORT DATE: 04/05/93 WORK UNIT # 1726

DETAIL SUMMARY SHEET

TITLE: Physiologic Assessment of Exercise Limitation in Upper Airway Obstruction

KEYWORDS: exercise, upper airway, lung mechanics

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC
ASSOCIATES: Becker, Gregory CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To examine the role of inspiratory muscle function in the limitation of exercise function.

TECHNICAL APPROACH

Patients with well defined upper airflow obstruction will have pulmonary function testing to determine resting inspiratory muscle function. Exercise testing will then be performed with monitoring of both inspiratory and expiratory airflow mechanics. The degree of inspiratory airflow reduction will be correlated with the degree of exercise limitation. Resting values will be used to derive predictors of exercise limitation.

PRIOR AND CURRENT PROGRESS

Four patients with upper airway obstruction have completed the protocol; none since FY-90. Additional patients are being recruited. It is anticipated that when technical assistance is available about four to six additional patients will be studied. The unique nature of the testing procedures makes technical help difficult to obtain.

CONCLUSIONS

Researchers plan to complete the protocol in the upcoming year.

REPORT DATE: 10/04/93 WORK UNIT # 1732

DETAIL SUMMARY SHEET

TITLE: Pleural Pressure Measurements in Normal Healthy Volunteers During the Administration of Nasal Continuous Positive Airway Pressure (NCPAP)

KEYWORDS: nasal CPAP, pleural pressure, esophogeal pressure

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 5,515 Total: $ 5,515

STUDY OBJECTIVE
The objective of this pilot study is to quantify the increase in pleural pressure due to nasal continuous positive airway pressure (NCPAP). This will be accomplished by measuring pleural pressure at several levels of NCPAP in normal healthy volunteers.

TECHNICAL APPROACH
To measure pleural pressure at different levels of NCPAP using the esophageal balloon technique and, in addition, to continuously record chest/wall and abdominal motion.

PRIOR AND CURRENT PROGRESS
Two subjects have been enrolled altogether; none this past year. No subjects have been enrolled since the first year of the study due to lack of technical support and changing priorities of the PI. The supplies and equipment bought with protocol funding were used to support several other approved research projects. A new protocol will be submitted if technical support becomes available and if the increase in pleural pressure due to NCPAP has not yet been quantified.

CONCLUSIONS
None.

REPORT DATE: 01/12/93 WORK UNIT # 1736

DETAIL SUMMARY SHEET

TITLE: Treatment of Pulmonary Sarcoidosis with High Dose Inhaled Triamcinolone Acetonide

KEYWORDS: sarcoidosis, triamcinolone acetonide, therapy

PRINCIPAL INVESTIGATOR: Poropatich, Ronald MAJ MC
ASSOCIATES: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of high dose inhaled triamcinolone acetonide compared with oral prednisone in the treatment of biopsy proven, symptomatic, pulmonary sarcoidosis with or without associated pulmonary symptoms.

TECHNICAL APPROACH

A prospective randomized double-blind, placebo-controlled study. Forty-four patients will be enrolled in the study and undergo laboratory evaluation comprised of biochemical testing and pulmonary function analysis, at initiation, and completion of the study period (duration 6 months). Monthly physician visits will be conducted to assess objective and subjective clinical response, monitor untoward side effects, and assess compliance with therapy. Three chest x-rays will be taken during the study period.

PRIOR AND CURRENT PROGRESS

Since April 1992, three patients have been enrolled into the study. Six patients have completed the study. There have been no untoward side effects noted and no patient withdrawals. Although data has not been statistically reviewed, objective and subjective improvements have been observed in both patients, with reports of decreased pulmonary symptoms and increased pulmonary function tests.

CONCLUSIONS

Preliminary results are encouraging in that all patients have improved under therapy. Since all results are still blinded, no conclusion can be made regarding the efficacy of high dose inhaled triamcinolone acetonide in the treatment of pulmonary sarcoidosis.

REPORT DATE: 03/01/93 WORK UNIT # 1737

DETAIL SUMMARY SHEET

TITLE: Predicting Exercise Responses in COPD Patients

KEYWORDS: exercise, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC
ASSOCIATES: Hnatiuk, Oleh MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the accuracy of descriptive models for oxygen consumption and exercise ventilation in COPD patients. Descriptive models for these parameters were previously developed at WRAMC. These models use values from resting pulmonary function tests to predict the parameters at maximum exercise.

TECHNICAL APPROACH

Perform exercise testing of patients and measurement of resting lung function tests. Generate predicted values using previous descriptive models and compare to observed values using statistical methods.

PRIOR AND CURRENT PROGRESS

Thus far, 66 patients have completed the protocol (20 during the past year). No adverse clinical events or complications have occurred during the course of this study. Data collection is progressing. No data analysis has been undertaken to date.

CONCLUSIONS

Protocol remains active in data collection phase.

REPORT DATE: 07/06/93 WORK UNIT # 1739

DETAIL SUMMARY SHEET

TITLE: VA Cooperative Study No. 316: Efficacy of Passive Immunization in the Prevention of Infection due to Klebsiella Pneumoniae and Pseudomonas Aeruginosa

KEYWORDS: antibody, Klebsiella, Pseudomonas

PRINCIPAL INVESTIGATOR: Eliasson, Arn MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of a polyclonal antibody preparation in the prevention of bacteremia and sepsis from Klebsiella and Pseudomonas.

TECHNICAL APPROACH
Patients admitted to the intensive care units who are likely to stay longer than 3 days, and who are not felt to be immediately preterminal, will receive the antibody preparation or a placebo in the form of albumin infusion. Endpoints will include blood cultures, other clinical parameters of infection, and death. This is a multicenter study involving 16 medical centers and anticipates an enrollment of 16,000 patients. An addendum was approved in September 1992 for an increased dose of polyclonal antibody. In July 1993 the IND was transferred from OTSG sponsorship to Swiss Serum and Vaccine Institute.

PRIOR AND CURRENT PROGRESS
During the past calendar year, 50 patients have been successfully enrolled in the revised protocol calling for a new increased dose of polyclonal antibody; 65 subjects have been enrolled altogether. The drug has been very well tolerated with only two possible drug effects (transient hypertension) and resulted in discontinuation of the drug infusion in these patients. No long-term sequelae were experienced. Walter Reed's ICU has been one of the most productive centers in the multicenter protocol. Patients will continue to be enrolled. The salaries of the study nurse coordinators is being provided by the Swiss Serum and Vaccine Institute, which should provide enough funding to continue work through 1993.

CONCLUSIONS
An interim analysis of data is planned by the study center in West Haven, CT in August 1993 to determine whether or not primary endpoints with statistical significance have been reached.

REPORT DATE: 07/22/93 WORK UNIT # 1740

DETAIL SUMMARY SHEET

TITLE: The Effect of Diltiazem on Pulmonary Gas Exchange in Patients with Chronic Obstructive Lung Disease at Rest, with Exercise, with Exposure to a Hypoxic Environment and during Sleep

KEYWORDS: Ca channel, COPD, gas exchange

PRINCIPAL INVESTIGATOR: Moores, Lisa CPT MC
ASSOCIATES: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the potential of calcium channel antagonists to blunt the pulmonary vasoconstrictive response to hypoxemia, thus lowering pulmonary vascular resistance, increasing ventilation-perfusion mismatching, and worsening hypoxemia.

TECHNICAL APPROACH

Prospective study in patients with severe airflow obstruction and mild hypoxemia -- all subjects undergo baseline studies of ABG, pulmonary function, resting cardiac output, and incremental cardiopulmonary exercise before and after two hours of acute administration of 60 mg diltiazem. Subjects are then randomly assigned to receive four weeks of either diltiazem or a placebo, 60 mg TID, at which time all tests are repeated 2 hours after a medication dose.

PRIOR AND CURRENT PROGRESS

No new patients have been studied in the past year. Fourteen patients meeting the above criteria have been completely studied altogether. Plans are to continue the study in an attempt to look at the cardiopulmonary effects of chronic diltiazem use during sleep.

CONCLUSIONS

Examination of the data from the first 14 patients reveals no effect of acute or chronic diltiazem use on cardiac output, oxygen delivery, pulmonary function, or exercise performance. There was a trend toward a protective effect of diltiazem on pulmonary gas exchange at altitude, which is being further investigated.

REPORT DATE: 10/15/92 • WORK UNIT # 1743

DETAIL SUMMARY SHEET

TITLE: Maximum Inspiratory Flow Rate as a Determinant of Maximum Voluntary Ventilation in Normal Patients and Patients with Obstructive Lung Disease

KEYWORDS: onary disease, pulmonary function test

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh CPT MC
ASSOCIATES: Dillard, Thomas LTC MC; Kumke, Kevin CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 660 Total: $ 660

STUDY OBJECTIVE

To examine the validity of previously developed methods for prediction of maximum voluntary ventilation (MVV) in normal patients and in patients with stable chronic obstructive pulmonary disease.

TECHNICAL APPROACH

Patients are recruited from the Pulmonary Disease Clinic based on results of prior pulmonary function tests. Testing protocol requires approximately 1 hour on one visit. Usual medications are maintained. Data collected include: height, weight, resting forced expiratory and inspiratory spirometry, maximum voluntary ventilation, peak airway pressures at the mouth, single breath diffusing capacity for carbon monoxide, oxygen saturation, and total lung capacity by dilution method.

PRIOR AND CURRENT PROGRESS

A total of 40 patients have been studied to date; 17 during the past year. There have been no serious or unexpected reactions associated with this study. Identification of eligible patients, procurement and enrollment continue. There is no direct benefit to the patients, unless the primary physician requests the results.

CONCLUSIONS

This study is ongoing. It is too early to analyze data.

REPORT DATE: 01/11/93 WORK UNIT # 1745

DETAIL SUMMARY SHEET

TITLE: Beta Agonist Bronchodilator Inhalation in Mechanically Ventilated COPD Patients: A Comparison of Nebulizer and Metered Dose Inhaler with IspirEase

KEYWORDS: inhaled bronchodilators, COPD, mechanical ventilation

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Phillips, Yancy COL MC; Andresen, Paul CRTT

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the optimal method for administering inhaled beta agonist bronchodilator medications to COPD patients requiring mechanical ventilation.

TECHNICAL APPROACH

Mechanically ventilated COPD patients will be studied as they are recovering from the condition(s) that exacerbated their chronic disease. Physiologic responses will be compared to inhaled metaproterenol, administered either via a metered dose inhaler or an updraft nebulizer. The study will be double-blinded and placebo-controlled. The protocol has not been modified since approval.

PRIOR AND CURRENT PROGRESS

During the past year, the researchers have observed that Walter Reed Army Medical Center treats very few patients who would be appropriate subjects for enrollment in this protocol. In fact, no patient has been invited to enroll in the protocol. Furthermore, since the protocol was written, the medical literature has clarified our hypothesis, and many hospitals now incorporate the use of metered dose inhaler delivered bronchodilators to ventilator patients as standard practice.

CONCLUSIONS

Propose termination of this protocol because of poor access to an appropriate number of potential study subjects and because the medical literature has answered the scientific question proposed.

REPORT DATE: 04/15/93 WORK UNIT # 1746

DETAIL SUMMARY SHEET

TITLE: Clinical Utility of Post-Thoracentesis Radiography

KEYWORDS: chest radiography, thoracentesis

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh MAJ MC
ASSOCIATES: Doyle, James CPT MC; Torrington, Kenneth LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To prospectively assess whether the routine use of post-thoracentesis chest radiography in asymptomatic patients without clinically apparent complications is warranted. The diagnostic utility of this practice has never been prospectively evaluated.

TECHNICAL APPROACH

Patients on the Medical Service undergoing thoracentesis are enrolled after thoracentesis is performed, and a procedure note is completed by the patients' ward physicians. A chest x-ray is then obtained and reviewed for evidence of pneumothorax. Once this is completed, the patient's chart is reviewed within 48 hours following thoracentesis to determine whether any complications have occurred. Also, the chart is reviewed to identify whether obtaining the chest x-ray altered clinical management.

PRIOR AND CURRENT PROGRESS

To date, 180 patients have been enrolled in the protocol (85 this past year). Six have had complications as a result of their procedure. However, this complication rate is well below that reported in the literature There have been no serious or unexpected adverse reactions as a result of this study.

CONCLUSIONS

Data collection is presently ongoing. Interim analysis is planned when 200 cases have been collected. This number is higher than expected due to the low complication rate at our institution.

REPORT DATE: 08/13/93 WORK UNIT # 1747

DETAIL SUMMARY SHEET

TITLE: Increased Use of Repeat Fiberoptic Bronchoscopy: Utility in Patients with Suspected Bronchogenic Carcinoma

KEYWORDS: RFB, fiberoptic bronchoscopy, suspected malignancy

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Poropatich, Ronald MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 3,003 Total: $ 3,003

STUDY OBJECTIVE

To document the increased use of repeat fiberoptic bronchoscopy (RFB) at Walter Reed Army Medical Center; to evaluate indications for repeat procedures; and to determine the value of RFB in patients with suspected carcinoma.

TECHNICAL APPROACH

This study will be a retrospective chart review of all patients undergoing bronchoscopy in the WRAMC Pulmonary Clinic between 1986 and 1990. Patients who have had two or more procedures will be identified and sorted on the basis of the indication for the repeated bronchoscopy.

PRIOR AND CURRENT PROGRESS

Bronchoscopy reports (1,598) from the period January 1986 through December 1990 were screened, resulting in 207 patients being identified as having undergone RFB during that time. The incidence of repeated procedures increased progressively from 11% in 1986 to 20% in 1990. The largest patient group (59%) for repeat bronchoscopies were patients with suspected or proven carcinoma. The second largest group was immunocompromised patients with pulmonary infiltrates. Data analysis has been completed, and the results have been published in Chest.

CONCLUSIONS

Use of RFB increased steadily from 1986-90, due primarily to its use in previously diagnosed cancer patients presenting with second primary lesions, pulmonary metastases, or progressive disease requiring therapeutic interventions, and in infected HIV patients. For patients with new suspected malignancies, RFB is often diagnostic when the initial procedure has shown endobronchial or submucosal tumor but biopsy specimens were nondiagnostic.

REPORT DATE: 08/13/93 WORK UNIT # 1748

DETAIL SUMMARY SHEET

TITLE: Utility of Fiberoptic Bronchoscopy in Stage I Bronchogenic Carcinoma

KEYWORDS: fiberoptic bronchoscopy, bronchogenic carcinoma, solitary pulmonary

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Kern, Joseph MAJ MC; Weidner, Sara CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 155 Previous FYs: $ 663 Total: $ 818

STUDY OBJECTIVE

To determine the value of performing fiberoptic bronchoscopy in patients presenting for evaluation of solitary pulmonary nodules suspicious for bronchogenic carcinoma.

TECHNICAL APPROACH

This study will be a retrospective chart review of patients bronchoscoped in the Walter Reed Army Medical Center Pulmonary Clinic as part of their preoperative evaluation for solitary pulmonary nodules. The study will correlate bronchoscopic and surgical findings to determine whether a preoperative diagnosis of malignancy affects patient operability or the duration of surgery. The study also will evaluate the incidence of occult, second primary malignancies of the upper and lower respiratory tract in patients with bronchogenic carcinoma

PRIOR AND CURRENT PROGRESS

Charts (191) of patients evaluated between January 1986 and December 1989 were selected for review, and a study population of 91 patients with solitary pulmonary nodules was reported. There were 72 patients with bronchogenic carcinoma, 7 with carcinoid tumors, and 12 with benign nodules. The study was presented at the 1992 International Conference of the American Thoracic Society, published in abstract form in the American Review of Respiratory Disease, and has been accepted for publication in Chest.

CONCLUSIONS

Preoperative fiberoptic bronchoscopy in patients with malignant solitary pulmonary nodules did not alter clinical staging, obviate the need for surgery, shorten the duration of surgery, or reveal a significant number of occult primary carcinomas of the upper or lower respiratory tract. Benefit of preoperative FB was not demonstrated.

REPORT DATE: 09/30/93 WORK UNIT # 1749

DETAIL SUMMARY SHEET

TITLE: Air Transport of Patients with Pulmonary Defects

KEYWORDS: altitude, hypoxia, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Phillips, Yancy LTC MC; Knutsen, Sara CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 155 Previous FYs: $ 0 Total: $ 155

STUDY OBJECTIVE

Hypotheses: Hypoxic gas inhalation at ground level produces arterial oxygen tension (AOT) comparable to acute altitude exposure in patients with abnormal lung function under conditions isobaric for oxygen partial pressure. AOT during normobaric and hypobaric hypoxia correlates with and may be predicted from pulmonary function tests and blood gases on room air at ground level before exposure. AOT on oxygen supplementation at altitude correlates with ground level values.

TECHNICAL APPROACH

The protocol will follow the following procedures: measurement of barometric pressure; insertion of arterial catheter into the radial artery; monitoring of blood pressure and pulse oximetery continuously; sampling arterial blood for blood gas tensions and co-oximetery; exposure of subjects to 15% oxygen; ascent to simulated altitude conditions of 8000 feet using hypobaric chamber; sampling of arterial blood gases; addition of oxygen supplementation; and sampling of arterial blood gases. One minute of step-test exercise will be performed on four occasions, followed by sampling of arterial blood gases.

PRIOR AND CURRENT PROGRESS

To date, 33 subjects have been enrolled; 4 during the past year. There have been no serious or unexpected adverse reactions. One abstract was published during the past year, dealing with the effect of supine versus upright posture on the degree of arterial hypoxemias. Posture is an important issue in the air transport of patients and the mass movement of casualties.

CONCLUSIONS

Posture has a definite affect on the degree of hypoxemia. However, at altitude conditions the effect of posture has less influence than at sea level.

REPORT DATE: 10/13/92 WORK UNIT # 1750

DETAIL SUMMARY SHEET

TITLE: A Double-Blind, Placebo Controlled, Group Comparative Study of the Effect of Tilade (Nedocromil Sodium, 4 mg) on Cough Experienced by Asthmatics

KEYWORDS: asthma, nedocromil sodium, cough (asthma)

PRINCIPAL INVESTIGATOR: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effect of inhaled nedocromil on the cough experienced by subjects with asthma.

TECHNICAL APPROACH
Symptom scores, pulmonary function testing, and methacholine challenge will be assessed in patients assigned to either active drug or placebo. Investigators will be blinded to treatment.

PRIOR AND CURRENT PROGRESS
This study was terminated without enrolling any subjects, and the study's sponsor was so notified in April 1992. Obtaining needed approval beyond WRAMC proved to be administratively too difficult and time consuming.

CONCLUSIONS
None.

REPORT DATE: 11/13/92 WORK UNIT # 1751

DETAIL SUMMARY SHEET

TITLE: Postoperative Pulmonary Changes Following Laparoscopic vs. Right Subcostal Cholecystectomy

KEYWORDS: postoperative spirometry, cholecystectomy

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Bilello, John MAJ MC; Hopkins, Terry SSG CRTT

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 1,154 Previous FYs: $ 0 Total: $ 1,154

STUDY OBJECTIVE

To compare postoperative pulmonary changes following cholecystectomy performed with two different surgical methods: laparoscopic cholecystectomy (LC) versus right subcostal cholecystectomy (RSC).

TECHNICAL APPROACH

Volunteers scheduled for cholecystectomy will be enrolled to compare preoperative with postoperative spirometry, chest x-rays, and arterial blood gases. The plan is to compare the traditional surgical method, RSC, with the recently introduced high tech method, LC. The original protocol has not been modified, but in 1992 the investigators found that very few Walter Reed Army Medical Center patients were operated on using RSC.

PRIOR AND CURRENT PROGRESS

As of this date, 26 of the originally projected 60 patients have been enrolled in the study. Twenty-four patients underwent LC. One patient began with LC but complications forced conversion to RSC, and one patient was operated on with RSC. The RSC group had only one patient and, therefore, has been deleted from data analysis. Preliminary data analysis performed with the aid of the Department of Clinical Investigation statisticians has shown statistically significant findings in the LC group. Therefore, in November 1992 efforts to enroll new patients were ceased. There have been no serious or unexpected adverse reactions in any patient. The one patient whose operation was converted from LC to RSC experienced severe postoperative pain and nausea and withdrew from the study the morning following surgery. No other patient was withdrawn.

CONCLUSIONS

Final conclusions are pending. However, this study has revealed a statistically and clinically significant fall in spirometry following LC. A final report will be submitted within 3 months. A similar protocol has been designed to study postoperative pulmonary changes following video assisted thoracic surgery.

REPORT DATE: 02/11/93 WORK UNIT # 1752

DETAIL SUMMARY SHEET

TITLE: Eucapnic Voluntary Hyperventilation as a Bronchoprovocation Technique: Comparison with Methacholine Inhalation in Asthmatics

KEYWORDS: bronchoprovocation, airway hyperreactivity, asthma

PRINCIPAL INVESTIGATOR: Hurwitz, Kenneth CPT MC
ASSOCIATES: Phillips, Yancy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 1,339 Previous FYs: $ 0 Total: $ 1,339

STUDY OBJECTIVE

To compare the sensitivity of eucapnic voluntary hyperventilation (EVH) to methacholine inhalation challenge (MIC) in asthmatic subjects. In addition, the effect of presenting these tests in sequence will be examined, and the results of these challenges will be correlated with symptoms, serum immunoglobulin E level, and serum eosinophil count.

TECHNICAL APPROACH

This study is a randomized, prospective crossover trial. There have been no modifications to the original protocol. Subjects will complete a pulmonary questionnaire; have blood drawn for serum IgE level, serum eosinophil count, serum caffeine, and serum theophylline level; and then undergo bronchoprovocation challenge testing with either eucapnic voluntary hyperventilation (EVH) followed by methacholine inhalation challenge (MIC) or MIC followed by EVH. They will then return on a subsequent day and undergo the challenges in the reverse order.

PRIOR AND CURRENT PROGRESS

To date, 17 subjects have completed the protocol. There have been no serious or unexpected adverse reactions. There has been no benefit to the subjects. A few subjects declined to participate in the second day of testing after completing the first day.

CONCLUSIONS

The sensitivities of EVH and MIC in detecting airway hyperreactivity were similar. Severity of symptoms correlated with response to EVH, but not to MIC. Response to MIC, but not EVH, correlated with serum IgE level (and perhaps to serum eosinophil count). When the tests are performed in sequence, MIC attenuates the response to EVH; it may be that EVH attenuates the response to MIC in very sensitive subjects.

REPORT DATE: 06/07/93 WORK UNIT # 1753

DETAIL SUMMARY SHEET

TITLE: Accuracy of Predicted Normal Values in Clinical Spirometry

KEYWORDS: spirometry, height, prediction equations

PRINCIPAL INVESTIGATOR: Parker, Joseph MAJ MC
ASSOCIATES: Dillard, Thomas LTC MC; Phillips, Yancy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 1,364 Previous FYs: $ 0 Total: $ 1,364

STUDY OBJECTIVE

To assess the impact of using a subject's stated normal height versus their measured height on the calculation of predicted normal values for spirometry and on the clinical interpretation of spirometry; and to evaluate the current practices of PFT labs in the Washington, D.C. area.

TECHNICAL APPROACH

Patients referred for spirometry will be evaluated by first asking subjects their height and then measuring their height and arm span. Each subject's predicted normal values for FVC and FEV1 will then be calculated using both stated and measured height. A postal survey of local civilian and military PFT labs will be conducted to determine current practices regarding ascertainment of height.

PRIOR AND CURRENT PROGRESS

During the first year, 210 subjects were enrolled, and complete data was collected on all patients. A survey of local PFT labs (civilian and military) was conducted with 25 responders. The data was analyzed with the help of the DCI statistician (Dr. Chang).

CONCLUSIONS

There were significant differences between stated and measured heights with the differences becoming progressively larger with increasing age. These differences created significant differences in the calculation of predicted normal values and would have influenced/changed the interpretation of spirometry in approximately 20% of those patients older than 60. Clinical labs frequently do not measure height (50%).

REPORT DATE: 06/06/93 WORK UNIT # 1754

DETAIL SUMMARY SHEET

TITLE: The Effects of Buspirone on Respiraton in Asthma Patients

KEYWORDS: buspirone, asthma, respiration

PRINCIPAL INVESTIGATOR: Kumke, Kevin, CPT MC
ASSOCIATES: Derderian, Sarkis LTC MC; Hamm, Carolyn PhD

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 1,950 Previous FYs: $ 4,981 Total: $ 6,931

STUDY OBJECTIVE
To examine the effect of the antianxiety medication buspirone on respiration.

TECHNICAL APPROACH
The effect of buspirone on respiration in outpatient asthmatics will be evaluated in a double-blind, randomized, crossover fashion. This evaluation will include a series of three overnight polysomnograms and three central respiratory control evaluations. The central respiratory control studies will measure patient response to changes in airway resistance, carbon dioxide, and hypoxia.

PRIOR AND CURRENT PROGRESS
There have been 14 patients enrolled in this study, and 10 of these 14 have completed the study process. There have been no serious or unexpected adverse reactions. One patient has withdrawn due to complaints of dizziness while on buspirone. The dizziness resolved when the medication was discontinued. Prior studies involving buspirone have reported a 9% incidence of transient dizziness. Until 14 subjects have completed the study, it would be premature to make any statements regarding benefit to patients.

CONCLUSIONS
Buspirone increases the mean latency to REM sleep but does not significantly alter sleep efficiency or the percent of sleep stages in stable asthmatics with severe chronic air flow obstruction.

REPORT DATE: 08/24/93 WORK UNIT # 1755

DETAIL SUMMARY SHEET

TITLE: Eucapnic Voluntary Hyperventilation (EVH) as a Bronchoprovocation Technique: Development of a Standardized Ventilatory Dosing Schedule, and an Analysis of the Refractory Period After EVH in Asthmatics

KEYWORDS: asthma, hyperventilation, exercise

PRINCIPAL INVESTIGATOR: Argyros, Gregory CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the optimal ventilatory dosing schedule for eucapnic voluntary hyperventilation (EVH) challenge, and to determine whether or not a refractory period exists after EVH challenge to subsequent bronchoprovocation with EVH in asthmatics.

TECHNICAL APPROACH
Subjects with a history of asthma will be seen at the Pulmonary Clinic on 5 separate days. On day one, they will be given two successive EVH challenges 1 to 2 hours apart. On the other 4 days, they will be given four different EVH challens where either the duration of the challenge or the minute ventilation will be altered.

PRIOR AND CURRENT PROGRESS
A total of 21 subjects have completed the study. There were no serious or unexpected adverse reactions.

CONCLUSIONS
There clearly is a refractory period after EVH challenge where the bronchospastic response to subsequent challenge is decreased. There is a significant difference in the bronchospastic response as the duration and minute ventilation of the challenge is altered. It appears that a 6 minutes challenge at a minute ventilation of 30 X FEV1 is the optimal challenge.

REPORT DATE: 09/08/93 WORK UNIT # 1756

DETAIL SUMMARY SHEET

TITLE: Presentation of Carcinoma Metastatic to the Thorax and the Diagnosis with Fiberoptic Bronchoscopy

KEYWORDS: intrathoracic metastases, fiberoptic bronchoscopy

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Argyros, Gregory MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 1,502 Previous FYs: $ 0 Total: $ 1,502

STUDY OBJECTIVE

To determine: 1) the clinical presentation of patients with malignancies metastatic to the lung, 2) the diagnostic utility of fiberoptic bronchoscopy, and 3) the primary site of malignancies metastasizing endobronchially or submucosally.

TECHNICAL APPROACH

This is a retrospective chart review. The records of fiberoptic bronchoscopies performed between 1987-91 will be reviewed to determine eligibility for inclusion in this study. Charts reviewed will be from Pulmonary, Medical Oncology, Infectious Disease, Thoracic Surgery, and Radiation Oncology Clinics, as well as pathology reports and inpatient and outpatient records.

PRIOR AND CURRENT PROGRESS

This study has been completed. A total of 1,853 records were reviewed, with 111 cases meeting inclusion criteria. Data revealed that patients with endobronchial and submucosal metastases are more likely to have pulmonary symptoms (cough, hemoptysis, and chest pain), and their chest x-rays are more likely to show atelectasis. Bronchoscopy has its highest yield in this patient group. The majority of patients with endobronchial metastases have Kaposi's sarcoma, lymphoma, adenocarcinoma, or sarcoma (KLAS). Patients with newly diagnosed esophageal carcinoma who have no symptoms of pulmonary disease do not benefit from preoperative bronchoscopic evaluation. Findings have been presented in abstract form, accepted for publication, and an additional manuscript is under review.

CONCLUSIONS

During the AIDS epidemic, the spectrum of malignancies metastatic to the thorax has changed and can be remembered by the mnemonic acronym "KLAS." Bronchoscopy is helpful for diagnosing patients with pulmonary symptoms or with radiographic evidence of atelectasis.

REPORT DATE: 09/09/93 WORK UNIT # 1757

DETAIL SUMMARY SHEET

TITLE: Centocor: HA-1A Efficacy in Septic Shock (CHESS) Trial

KEYWORDS: septic shock, HA1A

PRINCIPAL INVESTIGATOR: Eliasson, Arn LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of a monoclonal antibody called HA1A in the treatment of septic shock.

TECHNICAL APPROACH
This is a multi-center study. Patients with septic shock will be infused with the monoclonal antibody HA1A. They will be tracked for organ failure and death, comparing the treatment arm with a placebo arm.

PRIOR AND CURRENT PROGRESS
Before approval was obtained to begin this study at WRAMC, an intermin analysis of data gathered from the other centers revealed an excess of deaths in the treatment arm. Speculations abound about why that was the case, but no firm explanation for this finding has been reported to date.

CONCLUSIONS
This study has been terminated.

REPORT DATE: 03/03/93 WORK UNIT # 9280

DETAIL SUMMARY SHEET

TITLE: Sleep and Respiratory Control in Kyphoscoliosis

KEYWORDS: sleep, kyphoscoliosis, nocturnal oxygenation

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC
ASSOCIATES: Rajagopal, Krishnan LTC MC; Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 2,249 Previous FYs: $ 2,535 Total: $ 4,784

STUDY OBJECTIVE

To describe the hypercapnic and hypoxic rebreathing responses in kyphoscoliosis and to correlate these respiratory changes with the severity of the spinal deformity, as well as the frequency and severity of nocturnal oxygen desaturations as assessed by standard nocturnal polysomnography.

TECHNICAL APPROACH

Patients between 18 and 60 years of age without airflow limitations, or other disorders affecting respiratory function, will be selected using Cobb's Angle to determine the severity of kyphoscoliosis as mild, moderate, or severe. Each participant will be administered tests of full pulmonary function, arterial blood gas analysis, comprehensive rebreathing under hypoxic and hypercapnic conditions, and nocturnal polysomnography. Results will be compared recording the severity of the disease.

PRIOR AND CURRENT PROGRESS

Since one of the associate investigator's departure from orthopaedics, no new patients have been enrolled. The researchers plan to solicit the assistance of another orthopaedic associate, specifically one who has access to the Scoliosis Clinic. This will be critical in recruiting patients.

CONCLUSIONS

None to date.

REPORT DATE: 05/10/93 WORK UNIT # 3704

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Rheumatoid Arthritis

KEYWORDS: iontophoresis, rheumatoid arthritis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN, MSN

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Rheumatology Service APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis of the hand and wrist joints in patients with rheumatoid arthritis.

TECHNICAL APPROACH
Patients with rheumatoid arthritis with active synovitis of the hand joints are randomized to receive corticosteroids into the affected joints with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS
Over 50 joints from 33 different subjects have been entered into this study; 22 patients have been entered this past year. There has been no incidence of unexpected or adverse reactions. The data has been reviewed with Dr. Chang, DCI statistician. In summary, the injected joints and iontrophoresis joints improved significantly, but so did the sham joints. The significant improvement of the control group is probably related to the phenomena of naturally waxing and waning disease and the selection of study joints at a period of flare.

CONCLUSIONS
The current plan is to continue this protocol until a satisfactory number of control joints have been studied to determine if this pattern continues.

REPORT DATE: 05/10/93 WORK UNIT # 3705

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Osteoarthritis

KEYWORDS: iontophoresis, osteoarthritis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis of the hand and wrist joints in patients with osteoarthritis.

TECHNICAL APPROACH

Patients with osteoarthritis with synovitis of the hand joints are randomized to receive corticosteroids into the affected joints with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS

A total of four patients have been entered into this study; two this past year. This experience and the clinical use of of iontopheresis demonstrate that this will probably be an effective technique. The reason for slow patient accrual is two-fold: 1) iontophoresis double-blind studies are very time-consuming (and emphasis has been placed on two other iontophoresis protocols which are near completion, and 2) participation requires a major commitment of patient time. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

Patients will be gradually entered into this study. Accrual will accelerate as another iontophoresis protocol is brought to completion over the next few months.

REPORT DATE: 05/10/93 WORK UNIT # 3706

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Bursitis and Tendinitis

KEYWORDS: iontophoresis, bursitis, tendinitis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis, bursitis, and tendinitis.

TECHNICAL APPROACH

Patients with bursitis and tendinitis are randomized to receive corticosteroids into the affected musculoskeletal area with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS

Completed iontopheresis study of over 30 soft tissue areas from 30 individual patients; 21 subjects during this past year. There has been no incidence of serious or unexpected adverse reactions. Data have been reviewed with Dr. Chang, DCI statistician. The data demonstrate a significant improvement of various forms of bursitis and tendonitis with this technique compared to sham procedures in a double-blind controlled fashion. Review of data in consideration of publication establishes the need to increase the numbe. of studies in various soft tissue areas.

CONCLUSIONS

Preliminary data indicates that iontopheresis is effective in the treatment of bursitis and tendonitis. Further data is necessary to complete this study and ready it for publication. The major focus will be to complete this protocol first, and compare the findings to the two other related protocols.

REPORT DATE: 08/04/93 WORK UNIT # 3707

DETAIL SUMMARY SHEET

TITLE: A Study of Autoantibiodies to Neutrophil Integrin Proteins in Patients with Rheumatoid Arthritis

KEYWORDS: autoantibodies, rheumatoid arthritis, integrins

PRINCIPAL INVESTIGATOR: Hartman, Kip MAJ MC
ASSOCIATES: Wright, Daniel COL MC; Klipple, Gary COL MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1990

FUNDING: Current FY: $10,763 Previous FYs: $ 11,644 Total: $ 22,407

STUDY OBJECTIVE

To determine the incidence of autoantibodies to the neutrophil adhesion glycoproteins CD11b/CD18 in patients with rheumatoid arthritis, and to investigate the correlation of these autoantibodies with the occurrence of infections.

TECHNICAL APPROACH

After consent, patients seen in the Rheumatology Clinic with the diagnosis of rheumatoid arthritis will be given a questionnaire, followed by a physician interview, and a physical examination. Blood will be collected and sera evaluated for anti-neutrophil antibody activity by immunofluorescent flow cytometry; specific anti-CD11b/CD18 reactivity will be studied in an immunobead antigen capture assay. Sera positive for antibodies to these adhesion proteins will be further evaluated for effects on neutrophil adhesion and opsonin receptor functions.

PRIOR AND CURRENT PROGRESS

No new patients have been registered the past year on this study; 22 patients have been enrolled altogether. There have been no adverse reactions or patients withdrawn from the study. There has been no benefit to patients. The study remains open, pending evaluation of data and further study of serum specimens.

CONCLUSIONS

None.

REPORT DATE: 10/15/92 WORK UNIT # 3709

DETAIL SUMMARY SHEET

TITLE: Pathogenesis of Systemic Sclerosis: Role of Transforming Growth Factor-Beta

KEYWORDS: systemic sclerosis, TGF-beta

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $30,788 Previous FYs: $ 25,923 Total: $ 56,711

STUDY OBJECTIVE

To establish (1) the presence of TGF-B in the skin of patients with systemic sclerosis (SSc); (2) establish that peripheral blood mononuclear cells (MNC) from patients with SSc express more TGF-B than normal MNC; (3) compare TGF-B levels among patients at various clinical phases, and (4) determine the type of MNC that is primarily responsible for the production of TGF-B.

TECHNICAL APPROACH

Patients with an established diagnosis of SSc will be enrolled in this study. MNC from these patients' blood will be isolated by gradient centrifugation, and RNA will be extracted, run on agarose gels, and hybridized with TGF-B probe. Skin biopsy specimens will be strained with anti-TGF-B antibodies. Perivascular areas will be evaluated carefully. Clinical information will be collected.

PRIOR AND CURRENT PROGRESS

To date, skin biopsies collected prior to initiation of this study have been used and stained with anti-TGF-B antibodies. Skin from patients with SSc, but not from normal individuals, express the TGF-B1 and TGF-3 isoforms. These results show that TGF-B is involved directly in the accumulation of fibrous tissues in the skin of patients with SSc. In new specimens to be collected from now on, the presence of TGF-B (in conjunction with substances that are also involved in the production of fibrous tissue and the regulation of the production of TGF-B) will be determined. TGF-B mRNA was found in peripheral blood MNC, but only in negligible quantities. A more sensitive Northern hybridization assay is being developed.

CONCLUSIONS

TGF-B isoforms are present in the skin of patients with SSc, implying that it is involved in the pathogenesis of the disease. Further studies are in progress to establish whether other factors are also favored.

REPORT DATE: 11/16/92 WORK UNIT # 3710

DETAIL SUMMARY SHEET

TITLE: Effects of Anti-IgD-dextran Conjugates on Human B Lymphocyte Antibody Production

KEYWORDS: B lymphocyte, antibody, humoral immunity

PRINCIPAL INVESTIGATOR: Dennis, Greg LTC MC
ASSOCIATES: Katona, Ildy CAPT MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 7,712 Previous FYs: $ 12,383 Total: $ 20,095

STUDY OBJECTIVE

To examine the effects of anti-IgD-dextran conjugates on human B lymphocyte expression of B cell activation markers and adhesion molecules, and to examine the effects of anti-IgD-dextran conjugates on human B lymphocyte proliferation and antibody production in the presence or absence of lymphokines.

TECHNICAL APPROACH

Elutriated B cell-enriched fraction will be used as a cell source. B or T cells will be further purified by a negative selection method. Cell surface antigens will be determined by a fluorescence activated cell sorter. Antibody production will be measured by ELISA. In vitro lymphokine production by B or T cells will be measured by ELISA.

PRIOR AND CURRENT PROGRESS

B cells, which are initially dull or negative for the adhesion molecule LFA-1, showed a marked increase by day 3 after stimulation with anti-IgD-dextran. HLA-DR expression also increased two to five fold by day 3 after stimulation. No correlation was seen between LFA-1 and HLA-DR on individual B cells. Anti-Ig-stimulated B cells induced a consistent and reproducible increase in the percentage of T cells, which express HLA-DR.

CONCLUSIONS

These data indicate that T cell-independent cross-linking of surface Ig by anti-IgD-dextran increases B cell surface expression of adhesion molecules which may facilitate its subsequent interaction with T cells or NK cells.

REPORT DATE: 10/15/92 WORK UNIT # 3711

DETAIL SUMMARY SHEET

TITLE: Lymphocyte Abnormalities in Patients with Systemic Lupus Erythematosus

KEYWORDS: SLE, lymphocytes

PRINCIPAL INVESTIGATOR: Klipple, Gary COL, MC
ASSOCIATES: Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $20,729 Previous FYs: $ 26,334 Total: $ 47,063

STUDY OBJECTIVE

To study signal transduction abnormalities in lymphocytes from patients with systemic lupus erythematosus (SLE). Specifically, do T-lymphocytes from patients with SLE have altered mitogen-induced intracellular free calcium responses, and do T-cells from patients with SLE have altered mitogen-induced phosphoinositol metabolism?

TECHNICAL APPROACH

Lymphocytes are obtained from peripheral blood mononuclear cells (MNC) by gradient centrifugation. T-cell clones are established and characterized. Signal transduction studies are performed in both fresh T-lymphocytes and T-cell lines.

PRIOR AND CURRENT PROGRESS

T-cell clones have been successfully established from six patients with SLE. The clones were first characterized phenotypically by immunofluorescence staining using monoclonal antibodies. Most of the clones are of the CD-4 phenotype. Subsequently, we screened the clones for autoreactivity; i.e., ability to respond to autoantigens. Approximately 20 percent of the clones respond to self antigens. Autoreactive clones are now being tested for their ability to respond to anti-CD-3 antibodies by raising their intracellular free calcium concentration.

CONCLUSIONS

Autoreactive clones are established successfully from the peripheral blood of patients with SLE. Further characterization of the clones will give valuable information on their function and origin.

REPORT DATE: 05/17/93 WORK UNIT # 3712

DETAIL SUMMARY SHEET

TITLE: Autoreactive T Lymphocytes in the Pathogenesis of Systemic Sclerosis

KEYWORDS: systemic sclerosis, T cells, autoimmunity

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Tsokos, George MAJ MC; Sfikakis, Peter MD

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 8,387 Previous FYs: $ 27,429 Total: $ 35,816

STUDY OBJECTIVE

To determine the frequency of hypoxanthine phosphoribosyltransferase (HPRT) gene mutated T cells in the peripheral blood of patients with systemic sclerosis, and to determine whether HPRT gene mutated T cell clones derived from patients with systemic sclerosis demonstrate reactivity to the presumed scl-70 autoantigen.

TECHNICAL APPROACH

This is a one-time blood drawing study. Isolate T cells from the peripheral blood of patients with systemic sclerosis. Use a clonal assay to determine the frequency of HPRT gene mutated T cells. Expand in vitro T cell clones. Test their ability to proliferate in the presence of the scl-70 antigen.

PRIOR AND CURRENT PROGRESS

Results to date have demonstrated that the frequency of HPRT gene mutated T cells is increased in the peripheral blood patients with systemic sclerosis. A limited number of clones studied so far demonstrate increased proliferative responses to scl-70 antigen. A larger number of patients needs to be studied to identify possible correlations between clinical manifestations and the frequency of mutated T cells. A larger number of clones needs to be studied to establish the specificity of the reactivity patterns of the clones. Thirteen patients have been studied so far. There is no direct benefit to the patients. No unexpected or serious adverse effects have been noticed.

CONCLUSIONS

A clonal assay has become available to identify autoreactive, possibly pathogenic, T cells in patients with systemic sclerosis.

REPORT DATE: 06/14/93 WORK UNIT # 3713

DETAIL SUMMARY SHEET

TITLE: Antiphospholipid Antibody Syndrome (APAS): Role of Antiphospholipid Antibodies (APLA) and B2-glycoprotein (gp)-I in the Clinical Manifestations of APAS

KEYWORDS: antiphospholipid, B2-glycoprotein-I, thrombosis

PRINCIPAL INVESTIGATOR: Tesar, Joseph MD DAC
ASSOCIATES: Klipple, Gary COL MC; Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $14,220 Previous FYs: $ 0 Total: $ 14,220

STUDY OBJECTIVE

To define the relationship of antiphospholipid antibody (APLA) and B2-glycoprotein-I to clinical manifestations of arterial and venous thrombosis, platelet aggregation, thrombocytopenia, and livedo reticularis in patients with systemia lupus erythematosis (SLE) and other connective tissue disorders.

TECHNICAL APPROACH

The study is a prospective, randomized investigation of patients with SLE, other connective tissue disorders, and control subjects. Each patient's serum will be tested for APLA, ANA, Ds DNA, VDRL, lupus anticoagulant, and complement and immune complexes. All pertinent clinical manifestations will be dated and recorded. The enhancement (if any) of APLA binding to phospholipids by B2-glycoprotein will be determined in the first phase of the study.

PRIOR AND CURRENT PROGRESS

To date, this study has examined 30 samples of serum from patients with SLE and 30 samples of serum from controls for presence of APLA. A new method of isolation and purification of serum IgG free of contamination by B2-glycoprotein has been developed. APLA binding activity of 30 isolated IgG in a serum-free system has been examined, and a variable enhancement of APLA by B2-glycoprotein was found in an ELISA procedure. The relationship of these data to clinical manifestation is now being studied.

CONCLUSIONS

Isolated immunoglobulins with APLA activity are binding negative-charged phospholipids (cardiolipin) in the presence of B2-glycoprotein. B2-gylcoprotein enhances this binding activity, from insignificant to very substantial. This fact has important biological and possibly diagnostic applications.

REPORT DATE: 06/09/93 WORK UNIT # 3714

DETAIL SUMMARY SHEET

TITLE: Role of Adhesion Molecules in the Activation of T Cells From Patients with Systemic Lupus Erythematosus (SLE)

KEYWORDS: lupus, adhesion molecules, T lymphocytes

PRINCIPAL INVESTIGATOR: Oglesby, Robert CPT MC
ASSOCIATES: Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE. Jun 1992

FUNDING: Current FY: $ 2,886 Previous FYs: $ 1,271 Total: $ 4,157

STUDY OBJECTIVE

To assess the role of adhesion molecules in the pathogenesis of systemic lupus erythematosus (SLE), and to determine whether deficient adhesion molecule expression and function are responsible for the inability of SLE T cells to respond to recall antigens.

TECHNICAL APPROACH

T cells will be obtained from the peripheral blood of patients with SLE by Ficoll gradient centrifugation and sheep erythrocyte rosetting. T cells will be cultured in the presence of recall antigens, and in the presence of functional adhesion molecules.

PRIOR AND CURRENT PROGRESS

Blood has been drawn from 14 subjects. There has been no incidence of serious or unexpected adverse reactions. Isolated lupus T cells cultured under conditions where both first and second stimulatory signals are provided under optimal conditions demonstrate normal response to CD3-mediated stimulation. Lupus T cells respond poorly to recall antigens (tetanus toxoid, etc.) because the adhesion molecule-mediated co-stimulatory signal is deficient. The response of SLE derived T cells to recall antigens is normalized in the presence of functional adhesion molecule B7/BB1.

CONCLUSIONS

Deficient functioning of adhesion molecules that are expressed on the surface membrane of antigen presenting cells is responsible for the inability of lupus T cells to respond to recall antigens such as tetanus toxoid and influenza. These findings may explain why lupus patients are more prone to infections.

REPORT DATE: 07/12/93 WORK UNIT # 3715

DETAIL SUMMARY SHEET

TITLE: Metabolic Parameters in Systemic Lupus Erythematosus with Neuropsychiatric Manifestations

KEYWORDS: Lupus erythematosus, neuropsychiatric, metabolic parameters

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $29,592 Previous FYs: $ 0 Total: $ 29,592

STUDY OBJECTIVE

To establish the value of cerebrospinal fluid (CSF) metabolic parameters in the diagnosis of active central nervous system (CNS) disease.

TECHNICAL APPROACH

Patients will be evaluated clinically, and a neuropsychiatric evaluation will be completed. Levels of C5b-9, C3a C4, antineuronal antibodies, antiphospholipid antibodies, quinolinic acid, and interleukin 6 will be determined in the cerebrospinal fluid (CSF) of patients with systemic lupus erythematosis (SLE). The diagnosis and prognostic value of these parameters will be determined.

PRIOR AND CURRENT PROGRESS

This study has found that patients with SLE who have inflammatory CNS disease have significantly elevated levels of quinolinic acid. Three patients have been enrolled to date, with no serious or unexpected adverse reactions noted.

CONCLUSIONS

Elevated levels of quinolinic acid in the CSF of patients with lupus may be useful in determining the cause of neuropsychiatric manifestations in these patients.

REPORT DATE: 06/10/93 WORK UNIT # 7136

DETAIL SUMMARY SHEET

TITLE: An Investigation of Frontal Lobe Mediated Knowledge Representation

KEYWORDS: cognition, frontal lobe

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
1) To develop face valid and psychometrically constrained tests of executive functions guided by a preliminary neuropsychologically derived information processing model; 2) To obtain normal control data; 3) To motivate a more detailed and complete neuropsychological model of executive (frontal lobe) functions based on observed brain-behavior relationships; 4) To develop guidelines fo. the care of individuals impaired with clinical or "subclinical" executive function deficits.

TECHNICAL APPROACH
Patients will receive neurological and neuropsychological examinations at WRAMC and at NINDS, NIH.

PRIOR AND CURRENT PROGRESS
Twenty patients have been entered in the study (two during the past year) and have received baseline and q6 month evaluations at the NIH. There has been no incidence of serious and/or unexpected adverse reactions. Additional patients are are now being entered in conjunction with a concomitant brain tumor protocol.

CONCLUSIONS
Preliminary analysis of data, to date, supports the model of frontal lobe executive function hypothesized in the original protocol.

REPORT DATE: 03/01/93 WORK UNIT # 7141

DETAIL SUMMARY SHEET

TITLE: Recombinant Beta Interferon as Treatment for Multiple Sclerosis: A Multicenter Protocol

KEYWORDS: beta-interferon, multiple sclerosis

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the therapeutic efficacy of beta-interferon in multiple sclerosis.

TECHNICAL APPROACH
Patients will be administered 6 million units r-human beta-interferon intramuscularly weekly for 2 years and will then be followed for 1-2 years. During FY-93, there were some administrative protocol modifications and changes to the consent form. The changes were approved by the HUC/IRB in October 1992.

PRIOR AND CURRENT PROGRESS
Fifty-three patients have been entered at WRAMC (26 this past year). A total of 290 patients have been entered in the entire multicenter study (83 this past year). There have been no adverse experiences attributable to the drug.

CONCLUSIONS
R-human beta-interferon is safe and well tolerated when administered at a dose of 6 million units IM for over 1 year to patients with multiple sclerosis.

REPORT DATE: 03/15/93 WORK UNIT # 7142

DETAIL SUMMARY SHEET

TITLE: Intramuscular Poly-ICLC and CCNU in the Management of Malignant Gliomas: An Open Trial

KEYWORDS: poly-ICLC, CCNU

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Mar 1989

FUNDING: Current FY: $12,000 Previous FYs: $ 295 Total: $ 12,295

STUDY OBJECTIVE
To determine the toxicity and tolerance of low doses of poly-ICLC and CCNU in patients with malignant gliomas.

TECHNICAL APPROACH
Originally, patients were administered poly-ICLC at 10, 20, 50, and 100 mcgm/kg twice weekly for 1 year. The dosage schedule was changed in August 1992 by addendum and approved by the HUC/IRB. Currently, patients are receiving 15 mcg/kg three times a week (total 45 mcgm/kg/wk) for 36 months.

PRIOR AND CURRENT PROGRESS
Thirty-seven patients with malignant glioma have been entered to date; 16 during the past fiscal year. There was minimal or no toxicity. Nine patients on intermittent or short-term poly-ICLC have died, but 18 of 28 with 4 to 32 month MRI follow-up responded with regression or stabilization of enhancing tumor (median = 80% volume decrease). All anaplastic astrocytoma (AA) patients remain alive and well, and are off steroids or are on a taper a median of 27 months from diagnosis. Median glioblastoma (GBM) survival is now 16 months. (Historical median survival is 26 months for AA and 10 months for GBM). Optimum dose appears to be 10-20 mcg/kg IM two to three times weekly, yielding a 73% response rate (16/22). Tumor response appears associated with 2'5' OAS activation, but not with serum interferon, II-2, II-6, TNF, or Neopterin. The researchers hypothesize activation by poly-ICLC of a basic host tumor suppressor system.

CONCLUSIONS
Poly-ICLC can be safely administered to patients with malignant gliomas with virtually no toxicity over 18 months. Prolonged, quality survival with tumor regression on MRI in most patients suggests that a more extensive trial is warranted. The concept of long-term, broad spectrum stimulation of host defenses with nontoxic, inexpensive double-stranded RNAs such as poly-ICLC may be applicable to treatment of other aggressive malignancies.

REPORT DATE: 11/25/92 WORK UNIT # 7143

DETAIL SUMMARY SHEET

TITLE: Investigation of the Effectiveness of Nimodipine in Movement Disorders

KEYWORDS: Nimodipine, movement disorder, calcium channel blocker

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Nov 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effectiveness of calcium channel blocker Nimodipine in movement disorders.

TECHNICAL APPROACH
Patients with involuntary movement disorders (chorea, myoclonus, dystonia, tremor) will be enrolled. Each patient will be videotaped prior to treatment. Nimodipine 30 mg will be prescribed qid for 10 days. Patient's improvement will be evaluated by a clinical rating scale and a second videotape. An unbiased observer will rate the tapes.

PRIOR AND CURRENT PROGRESS
Thirty-three patients with a variety of movement disorders have been studied (23 during this past year). There were eight patients with torticollis, six with tremor, three with chorea, three with spinal myoclonus/myokymia, two with generalized dystonia, three with focal limb dystonia, three with tics, two with hemifacial spasm, two with painful legs/moving toes, and one with large fasciculation. All patients with cerebellar tremor showed remarkable improvement as seen in videotapes and clinical rating scales. One patient with myokymia of lower leg muscle showed significant improvement. No side effects were noted.

CONCLUSIONS
The calcium channel blocker drug nimodipine when given at a dose of 120 mg was effective in some patients with disabling cerebellar tremor.

REPORT DATE: 07/01/93 WORK UNIT # 7144

DETAIL SUMMARY SHEET

TITLE: A Controlled Efficacy Study of a Brief Multidisciplinary Brain Injury Rehabilitation Program in Moderately Head Injured Service Members

KEYWORDS: traumatic brain injury, moderate head injury

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effectiveness and cost efficiency of a comprehensive TBI rehabilitation program, compared to one providing only counseling and support; to determine and quantify the short/long-term neurologic and neuropsychologic consequences of moderate head injury in the Army and its impact on some aspects of military performance; and to develop and test a relatively brief neuropsychologic screen that is sensitive to and predictive of effects of minor/moderate head injury.

TECHNICAL APPROACH
Each subject will receive neurological, neuropsychological, psychiatric, and medical rehabilitation; EEG and evoked potential, and neuroophthalmologic testing; physical and occupational therapy; clinical psychiatry interview; and an MRI. Following the comprehensive evaluation, patients will be randomly assigned to one of two treatment groups. Patients will then be returned to duty and followed.

PRIOR AND CURRENT PROGRESS
Approval and funding have been obtained from DVA. with supplemental funding from DOD. Personnel have been hired and trained. Evaluation instruments have been developed, and data entry forms have been prepared. Approval for Traumatic Brain Injury (TBI) Special Treatment Service (STS) designation at WRAMC has been obtained. Thirty-three patients have been randomized into the study to date; 20 during this reporting period. An additional 12 patients have completed treatment as program patients. There was no incidence of serious or unexpected adverse reactions. Accessions are expected to accelerate with the new STS designation for TBI.

CONCLUSIONS
None.

REPORT DATE: 01/08/93 WORK UNIT # 7145

DETAIL SUMMARY SHEET

TITLE: Dysesthetic Pain: A Blinded and Controlled Study of Treatment with Capsaicin 0.075%

KEYWORDS: pain, capsaicin

PRINCIPAL INVESTIGATOR: Bolt, Jodie CPT MC
ASSOCIATES: Sinoff, Stuart MAJ MC

SERVICE: Neurology Service STATUS: Terminated
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 131 Previous FYs: $ 0 Total: $ 131

STUDY OBJECTIVE
To ascertain in the context of a double-blinded, placebo controlled study whether capsaicin 0.075%, when applied topically to the skin, will alleviate or improve burning, superficial dysesthetic pain caused by meralgia paresthetica, reflex sympathetic dystrophy (sympathetically maintained pain), burning peripheral neuropathies, or other non-specified neuropathic (burning) pain.

TECHNICAL APPROACH
This is a multi-center study. Patients will be randomly enrolled into the four groups delineated above. After an initial evaluation, patients will apply test ointment (cream) to affected areas four times daily for a 6 week period. They will return every 2 weeks for questioning and completion of a case report form. Patients will complete the case report forms at specified times at home, foregoing travel to Walter Reed every 2 weeks. These forms will be returned at the time of the conclusion visit (6 weeks).

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 12/14/92 WORK UNIT # 7146

DETAIL SUMMARY SHEET

TITLE: Investigation of Cardiac and Cerebrovascular Effects of the Diving Reflex

KEYWORDS: diving reflex, electrocardiogram, heart rate

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Leone, Leonard CPT MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To investigate the effect of sudden exposure of head and face to cold water, with or without breath-holding, on heart rate and brain waves.

TECHNICAL APPROACH
Twenty asymptomatic subjects and 20 patients with brain stem lesions will be studied. EEG, EKG and oxygen saturation will be recorded during 30 second epochs, including baseline, cold water applied to forehead, cold water applied to forehead and breath-holding, and Valsalva's maneuver.

PRIOR AND CURRENT PROGRESS
This study compared the change in heart rate resulting from breath-holding, cold compresses to the forehead, and both in six patients (five this past year) with well-circumscribed brain stem tumors, and in eight age-matched control subjects (five this past year). Patients with upper brain stem tumors and controls experienced either no change or decreased heart rate in response to the above stimuli. In contrast, patients with tumors involving the pontomedullary region experienced an increase in heart rate There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
This observation indicated that in humans isolated lesions involving the pontomedullary region can disrupt pathways mediating the diving reflex and lead to paradoxical tachycardia.

REPORT DATE: 04/22/93 WORK UNIT # 7147

DETAIL SUMMARY SHEET

TITLE: Investigation of the Localizing Value of Clinical Signs Observed During Epileptic Seizures

KEYWORDS: epilepsy, seizure, electroencephalography

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 1,048 Previous FYs: $ 1,744 Total: $ 2,792

STUDY OBJECTIVE

To identify those clinical signs and symptoms during an epileptic seizure with localizing value; i.e., indicating the region of the brain from which the seizures begin. Such localizing signs are very important in clinical or surgical management of patients with intractable seizures.

TECHNICAL APPROACH

All videotapes of seizure patients admitted to the Neurology Service over the past 5 years will be reviewed. These tapes include both behavioral seizures and concurrent recorded brain waves during seizures. The films will be observed for a number of clinical signs (e.g., head turning, dystonia, etc.) and recorded on a data sheet included in the protocol. The concurrent electrical brain discharges will be studied in relation to the patient's behavioral seizures.

PRIOR AND CURRENT PROGRESS

A total of 100 tapes of seizures were reviewed on 30 patients with respect to a clinical sign termed dystonia. Since the last reporting year, 19 tapes from 8 patients have been reviewed. Dystonia was seen in 8 of 30 (26%) patients (average four seizures per patient). All seven patients with unilateral dystonia demonstrated it contralateral to the discharging focus; one patient had alternating dystonia, but the first dystonic limb was contralateral to the area of the brain damage. Currently, the localizing value of "head turning" during seizures is being evaluated.

CONCLUSIONS

Epileptic dystonia is an important localizing sign when it occurs during a seizure. It points to the contralateral hemisphere as being the side of pathology.

REPORT DATE: 11/11/92 WORK UNIT # 7148

DETAIL SUMMARY SHEET

TITLE: Computer Modelling of Pupillary Light Reflexes

KEYWORDS: computer modelling, pupillary defects

PRINCIPAL INVESTIGATOR: Gunderson, Carl COL MC
ASSOCIATES: Rosenberg, Michael LTC MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To utilize clinical and laboratory data gathered from normal subjects and patients with afferent pupillary defects to train, test, and formulate a neural network model of pupillary function.

TECHNICAL APPROACH
This study will review 50-100 charts of patients who have had infrared television pupillometry (ITP) studies, either normal or abnormal, as part of their evaluation in the Neuro-Ophthalmology Clinic.

PRIOR AND CURRENT PROGRESS
There has been very little progress to date. ITP has not been available because the hardware, on loan from the company, has either been nonfunctional or absent for repairs. It has returned to the Ophthalmology Clinic this month, and pupillography studies are now being done. It will take many months to compile enough studies to consider setting up a neural network with the appropriate training data.

CONCLUSIONS
Very little data has been collected, the network has not been designed, and no conclusions can be drawn at this time.

REPORT DATE: 07/29/93 WORK UNIT # 7149.

DETAIL SUMMARY SHEET

TITLE: Investigation of the Yield of Magnetic Motor Evoked Potentials in Neurosurgical Disorders: Spinal Cord and Posterior Fossa Lesions and Hydrocephalus

KEYWORDS: spinal cord, evoked potentials, magnetic stimulation

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Osenbach, Richard MAJ MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the usefulness of magnetic motor evoked potentials as a diagnostic test in spinal cord disorders, posterior fossa lesions, and hydrocephalus.

TECHNICAL APPROACH
This protocol is approved by FDA for enrollment of patients with spinal cord disorders and control subjects. Fifty patients with spinal cord disorders and 30 control subjects will be recruited. The integrity of the motor system will be evaluated by stimulating the scalp by a magnetic stimulator of 1.5 tesla strength and recording the response from different hand and leg muscles. Further areas of stimulation will include the posterior cervical region at C6, Erb's point and wrist, or popliteal fossa. Presence and absence of motor responses as well as absolute cortical conduction time and central conduction times will be compared with that of controls.

PRIOR AND CURRENT PROGRESS
To date, 10 patients with spinal cord disorders have been studied. Magnetic motor evoked responses have been abnormal in 9 of 10 patients.

CONCLUSIONS
Magnetic motor evoked potential tests have been abnormal in 90% of the patients with spinal cord disorders. This test may prove to be a valuable tool for evaluation of patients suspected to have spinal cord pathology.

REPORT DATE: 09/15/93 WORK UNIT # 7150

DETAIL SUMMARY SHEET

TITLE: Investigation of the Effectiveness of Botulinum Toxin-A Against Increased Muscle Tone

KEYWORDS: botulinum toxin-A, spasticity, rigidity

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effectiveness of botulinum toxin-A against spasticity and rigidity.

TECHNICAL APPROACH
This is a double-blind crossover study of botulinum toxin-A versus normal saline. Patients' degree of spasticity or rigidity will be rated prior to the first injection by a neurologist blinded to the order of injections. If the first injection does not produce any improvement after 2 weeks, then the second agent will be administered. If improvements are seen within the first 2 weeks, the second injection will be delayed for 3 months.

PRIOR AND CURRENT PROGRESS
To date, 13 patients (7 rigidity, 6 spasticity) have had completed evaluations. All seven patients with spasticity demonstrated a significant response to botulinum toxin-A (improvement of two or more rating steps), and five of seven patients with rigidity also disclosed this degree of improvement. In the rigidity group significant improvement was noted in three patients with progressive supranuclear palsy and in two patients with Parkinson's disease.

CONCLUSIONS
Botulinum toxin-A alleviates rigidity and spasticity in most patients with neurological disorders. Regular administration of this drug reduces pain, helps nursing, and facilitates physical therapy of these patients.

REPORT DATE: 07/07/93 WORK UNIT # 9200

DETAIL SUMMARY SHEET

TITLE: Anatomical and Functional Sequelae of Head Injuries Incurred in Vietnam

KEYWORDS: penetrating head injury, post traumatic epilepsy, neuropsychological

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Jun 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 6,875 Total: $ 6,875

STUDY OBJECTIVE
To examine selected veterans who received head injuries in Vietnam, plus Vietnam veterans who received no head injuries as a control group.

TECHNICAL APPROACH
Each subject will receive a neurological exam, CT scan, speech pathology exam, motor exam, audiology exam, electrophysiology battery, and neuropsychological exam. In addition, an American Red Cross caseworker has interviewed each subject and family to complete a field study.

PRIOR AND CURRENT PROGRESS
Inpatient phase completed as of October 1984. Contact is maintained with VHIS subjects, and selected patients are reevaluated at WRAMC periodically. Data analysis continues. Recent analyses have centered on return to work after penetrating head injury. Fifty percent of our population is employed; return to work can be predicted from analysis of neurologic and cognitive status. Additional data analysis will continue for many years, but new patient examinations are not contemplated under this protocol. Thus, formal termination of this protocol is requested.

CONCLUSIONS
The VHIS database represents an invaluable asset on computer tape and microfiche that will continue to provide room for analysis for years to come. While many of the questions posed in the original protocol have already been answered, new and often more exciting questions have arisen and will continue to arise as investigators explore the data.

REPORT DATE: 12/16/92 WORK UNIT # 7521

DETAIL SUMMARY SHEET

TITLE: Pregnancy Attitudes, Ambivalence and Symptom Distress

KEYWORDS: pregnancy attitudes, ambivalence, symptom distress

PRINCIPAL INVESTIGATOR: Rich, Irene LTC AN

DEPARTMENT: Department of Nursing **STATUS: Ongoing**
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop and test a self-report questionnaire which measures levels of ambivalence and general pregnancy attitudes of women during pregnancy; and to explore the relationships between psychological symptom distress, ambivalence, and general pregnancy attitudes during the trimesters of pregnancy.

TECHNICAL APPROACH
Women in the Obstetric Clinic will be sent study questionnaires in a prepaid mailer.

PRIOR AND CURRENT PROGRESS
Data collection is complete. Data analysis of the quantitative portion of the study is complete. Qualitative data analysis is nearly complete. It is anticipated that this work will be complete and an article prepared for publication by March 1993.

CONCLUSIONS
The Pregnancy Questionnaire is an 86-item instrument with coefficient alphas of 0.97 for the general pregnancy scale and 0.98 for the ambivalence scale. The tool is appropriate for use in research where pregnancy attitudes and ambivalence are of interest.

REPORT DATE: 02/19/93 WORK UNIT # 7522

DETAIL SUMMARY SHEET

TITLE: A History of Walter Reed Army Medical Center: 1909-1990

KEYWORDS: medical history, WRAMC

PRINCIPAL INVESTIGATOR: Sarnecky, Mary LTC AN

DEPARTMENT: Department of Nursing STATUS: Completed
APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To produce an accurate, up-to-date, scholarly history of Walter Reed Army Medical Center.

TECHNICAL APPROACH
This study used the historical methodology. A problem statement, conceptual framework, and study questions will be articulated. Data will be collected and assessed for validity and reliability. The data will be organized, integrated, analyzed, and synthesized as well. A research report will be written, and a manuscript will be prepared and submitted for publication. No modifications to the approach specified in the original protocol have been employed.

PRIOR AND CURRENT PROGRESS
This study is now complete. The research report has been written and all research is complete.

CONCLUSIONS
Findings reveal that Walter Reed Army Medical Center has had an illustrious history; consistently a premier institution in the vanguard of scientific advances. WRAMC's contribution to both military and civilian medicine has been significant.

REPORT DATE: 04/05/93 WORK UNIT # 7523

DETAIL SUMMARY SHEET

TITLE: Families Coping with Combat Injury

KEYWORDS: family coping, combat injury

PRINCIPAL INVESTIGATOR: Reeder, Jean LTC AN
ASSOCIATES: Tijerina, Maria LTC AN; Swartz, Ann MAJ AN

DEPARTMENT: Department of Nursing

STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe the family-related, patient-related, and injury-related variables to determine how they influence the way that families cope with combat injury.

TECHNICAL APPROACH
Data were collected three times from two family members of combat injured soldiers hospitalized at WRAMC: (1) within 1 week after the family arrived at WRAMC to visit the injured family member; (2) 1 month after the completed the first questionnaire; and (3) 1 year following administration of the first questionnaire. Families were asked to complete four questionnaires that measured: family coping, family perception of the injury event, family member perceived stress, and family "pile-up" of the file events.

PRIOR AND CURRENT PROGRESS
Data collection on this longitudinal study is complete. Due to significant attrition of subjects from n=25 to n=6, consultation was sought to revise data analysis, which is nearly complete. There were no serious and/or unexpected adverse reactions; however, the family members who responded on round 3 had anger, resentment, and frustration with respect to support provided to their injured family member.

CONCLUSIONS
Family coping strategies are modified over time from the beginning of a combat injury trajectory to a year later. Emotional symptoms of perceived stress attenuate over time. Family life events change among some respondents, typically increasing over time. Findings should not be generalized to all combat injured families because of the small sample size.

REPORT DATE: 04/12/93 WORK UNIT # 7525

DETAIL SUMMARY SHEET

TITLE: Determinants of Effective Coping and Adaptation Among Army Medical Department Soliders During Operation Desert Storm

KEYWORDS: adaptation, coping, causal models

PRINCIPAL INVESTIGATOR: Gurney, Cynthia LTC AN
ASSOCIATES: Biskey, Valerie COL AN; Sarnecky, Mary LTC MC

DEPARTMENT: Department of Nursing

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 29 Total: $ 29

STUDY OBJECTIVE

To identify determinants of effective coping and adaptation to the combat environment for Army Medical Department personnel. Through this, the AMEDD may design training, policy, and instructions that will ease the transition to combat in future conflicts.

TECHNICAL APPROACH

A questionnaire will be mailed to survey Army Medical Department soldiers (officer and enlisted, active duty and reserve components) who served in Southwest Asia during the Gulf War. US Army Personnel Information Command (PERSINSCOM) will provide the data base from which to sample this population. Following data collection, statistical analysis will include descriptive statistics, factor analysis, multi-group analysis, and, finally, causal modeling using path analysis. A total of approximately 2800 enlisted and 2500 officer personnel will be sampled.

PRIOR AND CURRENT PROGRESS

Over the past year, 1,310 usable responses were returned. The quantitative and qualitative data have been separated. Scan sheets have been read, and files of raw data and the data element have been created. Descriptive statistics are now available. A plan has been prepared for analyzing the qualitative data. Based on preliminary data entry, over 600 pages of qualitative data will be available for content analysis.

CONCLUSIONS

This is an ongoing study; no conclusions have been reached yet.

REPORT DATE: 07/12/93 WORK UNIT # 7526

DETAIL SUMMARY SHEET

TITLE: The Effect of a Self Learning Module for Cancer Pain Management on Nurses' Knowledge, Interventions, and Pain Relief for Cancer Patients

KEYWORDS: pain, knowledge, intervention

PRINCIPAL INVESTIGATOR: Petrov, Jean RN MS
ASSOCIATES: Reeder, Jean COL AN

DEPARTMENT: Department of Nursing

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 946 Previous FYs: $ 0 Total: $ 946

STUDY OBJECTIVE

To test the effectiveness of a nursing self-learning module for cancer pain management on: nurses' knowledge of cancer pain management, nurses' interventions for pain, and patients' pain relief.

TECHNICAL APPROACH

An experimental pretest/posttest design will be used to compare the effect of the self-learning module (SLM) on pain management knowledge of two groups of nurses from six wards. Wards will be matched according to nurse demographic and pretest data, then randomized for nurses to receive the treatment (SLM) or not. The effect of the SLM on nurse interventions and pain relief will be determined by the accrual of two 20 patient sets (pre and post use of SLM). Interventions will be taken from nursing documentation, and pain relief will be recorded from patient use of visual analogue scales to measure pain intensity.

PRIOR AND CURRENT PROGRESS

Nurse knowledge data collection was completed by July 1992; 42 nurses (21 in each group) were enrolled. Data collection had also been completed on the pre-SLM set of 20 patients by July 1992. Recruitment for the post-SLM set of patients was completed this past year with the addition of two patients; total enrollment has been 42 (21 in each group). One patient in each group was not used in the data analysis due to lack of pain intensity data and nurse intervention data. There were no serious or unexpected adverse reactions. Pain intensity scores were lower (mean scores after scores were averaged for each patient), and patients may have benefited from the knowledge they gained by participating. A manuscript is being written.

CONCLUSIONS

Nurses who received the SLM showed significantly greater improvement in test scores (15 +/- 8.2) compared to control nurses (-0.4 +/- 5.8), $t=-6.98$, $p=0.00005$. There were no significant differences in number of interventions per patient per day as monitored for each group. Pre- and post-SLM scores were 2.35 +/- 1.41 and 2.79 +/- 1.52, respectively. Pain intensity was significantly lower after PRN medications were given for post SLM patients.

REPORT DATE: 01/25/93 WORK UNIT # 7527

DETAIL SUMMARY SHEET

TITLE: Use of an Indwelling Peripheral Catheter for 3-5 Days Sequential Chemotherapy Doses in the Outpatient Setting

KEYWORDS: peripheral IV catheters, Heplocks, sequential chemotherapy

PRINCIPAL INVESTIGATOR: Shotkin, Jane RN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To observe the efficacy and safety of placing peripheral intravenous catheters in outpatients for 3-5 days while receiving daily doses of chemotherapy.

TECHNICAL APPROACH
A #22 gauge Insyte catheter will be inserted into either forearm of the patient and Heplocked. This catheter will be used daily to administer chemotherapy for a period of 3-5 days. The condition of the IV site and the ability to use the Heplock are charted daily.

PRIOR AND CURRENT PROGRESS
Thirty-three of the 100 patients scheduled to be in this study have been entered to date. No serious or unexpected adverse reactions have been noted. Data has not been compiled.

CONCLUSIONS
No conclusions.

REPORT DATE: 07/22/93 . WORK UNIT # 7528

DETAIL SUMMARY SHEET

TITLE: Evaluation of Care Cuisine Software

KEYWORDS: dietary behavior, software program, cancer

PRINCIPAL INVESTIGATOR: Jacobs, Mark MA

DEPARTMENT: Department of Nursing STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
CARE CUISINE is a Cancer Risk Reduction Education software program which focuses on how to learn low-fat, high-fiber eating habits that according to the National Cancer Institute may reduce the risk of developing certain cancers. This study will evaluate the effectiveness of CARE CUISINE.

TECHNICAL APPROACH
Fat and fiber intakes will be measured by using a Self-Reported Dietary Assessment program. This is a software program using a questionnaire format whereby an individual utilizes a computer keyboard to enter information concerning one's dietary behavior.

PRIOR AND CURRENT PROGRESS
Fifty-three participants filled out the initial application form. Forty-two completed the Self-Reported Dietary Assessment (SRDA). Fifty started the initial session. Thirty-four completed both the SRDA and the entire seven sessions. Therefore, the diets of 34 participants were assessed before and after CARE CUISINE intervention using a repeated measures design. Those individuals with baseline intakes of more than 30% of calories from fat decreased their intakes from a mean of 37.5% to 27.3% after intervention. Individuals with fiber intakes of less than 20 grams per day increased from a mean of 14.4 to 21.4 grams.

CONCLUSIONS
Changes in fat and fiber consumption were found to be statistically significant in the appropriate direction; i.e., a decrease in fat and an increase in fiber intake, including impressive results when dietary changes were analyzed separately for individuals who had not met the dietary guidelines before intervention.

REPORT DATE: 07/14/93 WORK UNIT # 9304

DETAIL SUMMARY SHEET

TITLE: The Effect of Altered Meal Patterns on Dietary Intake of Nurses

KEYWORDS: shift work, nurses, meal patterns

PRINCIPAL INVESTIGATOR: Reed, Judith LTC SP
ASSOCIATES: Reeder, Jean LTC MC

SERVICE: Nutrition Care Directorate STATUS: Completed
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the association of shift work on nurses' nutrient intake, meal patterns, satisfaction with work schedule, and perception of personal health.

TECHNICAL APPROACH
Nurses who work day, evening, night, and rotating shifts will be included and asked to complete a survey. Dietary recall data will be analyzed statistically using NOVA and chi square to evaluate differences among the four shift groups: day, evening, night, and rotating.

PRIOR AND CURRENT PROGRESS
Data collection began July 1992 and was completed in October 1992. Statistical analysis was completed in February 1993. The results are currently being compiled for publication.

CONCLUSIONS
Statistically significant differences were found among the groups on both satisfaction with personal health and with personal work schedule. No statistically significant differences were found in nutrient intake.

REPORT DATE: 06/01/93 WORK UNIT # 4262

DETAIL SUMMARY SHEET

TITLE: A Multicenter Randomized Trial of Adjuvant Cisplatin/Bleomycin Plus Whole Pelvis Irradiation Vs. Cisplatin/Bleomycin Alone in High Risk Stage IB and IIA Carcinoma of the Cervix

KEYWORDS: carcinoma, cervix

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology

STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To evaluate the effect of adjunctive pelvic irradiation added to adjunctive chemotherapy for high risk Stage IB and IIA cervical cancer as measured by progression-free interval and survival; and b) To compare the relative toxicities of two regimens with respect to serious complications and/or side effects.

TECHNICAL APPROACH

To be eligible, patients must have had a radical hysterectomy with pelvic and para-aortic lymphadenectomy for Stage IB or IIA cervical carcinoma. They must have one or more of the following poor prognostic signs: nodal metastasis, parametrial involvement, positive surgical margin, tumor diameter greater than 4 cm, deep cervical invasion, adenocarcinoma, adenosquamous carcinoma, or small cell histologic type. Patients are randomized to receive postoperative chemotherapy alone or chemotherapy plus pelvic irradiation.

PRIOR AND CURRENT PROGRESS

To date, 72 patients have been entered into this study; none this past year. Walter Reed has entered eight patients. No significant toxicity has been reported thus far.

CONCLUSIONS

Too early.

REPORT DATE: 01/06/93 WORK UNIT # 4304

DETAIL SUMMARY SHEET

TITLE: Evaluation of Inflammatory Pap Smears

KEYWORDS: pap, inflammation

PRINCIPAL INVESTIGATOR: Farley, John CPT, MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether inflammatory pap smears predict cervical dysplasia and if they can be treated clinically.

TECHNICAL APPROACH
Patients with inflammatory pap smears will be treated expectantly with antibiotics, sulfa cream, or culture. Pap smear will be repeated after treatment. If inflammation persists, colposcopy will be performed. Another pap smear will be obtained 1 year following the original one.

PRIOR AND CURRENT PROGRESS
Sixty-four patients have been enrolled, to date, without adverse reactions. Preliminary data reveals no difference between treatment approaches.

CONCLUSIONS
Ongoing determination.

REPORT DATE: 04/14/93 WORK UNIT # 4306

DETAIL SUMMARY SHEET

TITLE: GOG 132 A Phase III Randomized Study of Cisplatin Versus Taxol Versus Taxol and Cisplantin in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma

KEYWORDS: cisplatin, Taxol, ovarian

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the relative efficacy, survival, and toxicities of chemotherapeutic regimens consisting of cisplatin versus Taxol versus a combination of both drugs in patients with suboptimally debulked Stage III and IV epithelial ovarian cancer.

TECHNICAL APPROACH
After complete staging surgery, patients are randomized to receive six courses of cisplatin or Taxol or cisplatin and Taxol. Following therapy, if the patient is clinically free of disease, surgical reassessment will be performed.

PRIOR AND CURRENT PROGRESS
A total of 252 patients have been entered on this protocol from all GOG institutions. WRAMC has entered four patients. Patient accrual is ongoing as of April 1993.

CONCLUSIONS
Too early.

REPORT DATE: 06/11/93 WORK UNIT # 4307

DETAIL SUMMARY SHEET

TITLE: The Role of the P53 and Rasw Oncogenes in the Development of Malignant and Premalignant Lesions of the Female Genital Tract

KEYWORDS: p53 gene, Ras gene, gynecologic cancers

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the incidence of p53 and Ki-ras gene mutations in a series of gynecologic neoplasms which span a clinicophathologic spectrum ranging from benign to malignant.

TECHNICAL APPROACH

Cases for analysis will be selected after review of clinical records. Paraffin embedded tissues will be obtained. The blocks will then be sectioned and reviewed histologically. DNA will then be extracted from a tissue section and analyzed for the presence of mutation of the p53 and Ki-ras genes using polymerase chain reaction, design RFLP analysis, PCR/SSCP, and DNA sequencing.

PRIOR AND CURRENT PROGRESS

To date, no patients from WRAMC have been accrued to this study. A parallel study conducted by the PI has recently been completed at NNMC. In this study 20 ovarian cystadenomas, 20 low malignant potential (LMP) tumors of the ovary, and 23 ovarian carcinomas were analyzed. Based on the pattern of mutations identified, LMP tumors do not appear to be precursor lesions of ovarian cancer, but instead may be separate biologic entities.

CONCLUSIONS

Low malignant potential tumors of the ovary are distinct from ovarian carcinoma. Further study of these tumors, as well as other gynecologic neoplasms, is planned. Accrual of WRAMC cases in 1993 is anticipated.

REPORT DATE: 01/11/93 WORK UNIT # 4113

DETAIL SUMMARY SHEET

TITLE: Cooperative Gynecologic Oncology Group

KEYWORDS: gynecologic, oncology, group

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jan 1974

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, consisting of 40 major medical centers in the country who are interested in the area of gynecologic tumors and the treatment of gynecologic cancer. The GOG is recognized and funded through the National Cancer Institute.

TECHNICAL APPROACH
Walter Reed is active in approximately 40 GOG protocols. Presently, there are 60 protocols that are either active or continue to provide significant data. These protocols involve treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, uterine sarcoma, vulvar carcinoma, and gestational trophoblastic disease.

PRIOR AND CURRENT PROGRESS
Approximately 832 patients have been entered into GOG protocols from Walter Reed. There have been 34 patients entered since the last report. Since this is a Master Protocol, information about possible serious or unexpected adverse reactions will appear in the individual study APR's.

CONCLUSIONS
Detailed in individual reports.

REPORT DATE: 03/31/93 WORK UNIT # 4163

DETAIL SUMMARY SHEET

TITLE: GOG 26C: A Phase II Trial of Cis-platinum in the Treatment of Advanced Gyn Cancer

KEYWORDS: cis-platinum, diaminedichloroplatinum, gynecologic cancer

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1979

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of cis-platinum in the treatment of advanced or recurrent gynecologic cancers. A rejection type design will be used involving the fixed sample size of 25 disease patients per disease site per drug or drug use in the study. The design allows replacement of ineffective regimens by newer agents or combinations.

TECHNICAL APPROACH
Cis-platinum appears to exert its cytotoxic action by cross-linking DNA and thus acting in a manner similar to the bifunctional alkylating agents. It has demonstrated activity in animal studies against transitional cell carcinoma in mice. Toxicity in animals reveals myelosuppression, lymphoid atrophy, hemorrhagic enterocolitis, renal tubular necrosis, and cochlear damage, as well as some degree of immunosuppression.

PRIOR AND CURRENT PROGRESS
There have been 595 patients entered into this protocol for the entire GOG; (22 during the past year); 10 have been entered from WRAMC (3 during the past year). This protocol is closed to patients with squamous and nonsquamous cell carcinoma of the cervix, epithelial ovarian carcinoma, uterine sarcomas, endometrial adenocarcinomas, vaginal carcinomas, vulvar carcinomas, and first-line uterine sarcomas and endometrial adenocarcinomas. There has been one grade 4 renal toxicity, one grade 4 neurotoxicity, and one grade 4 GU toxicity.

CONCLUSIONS
Cis-platinum is active as first-line therapy in cervical squamous cell carcinoma, endometrial cancer, and mixed uterine mesosdermal sarcomas, and as second-line therapy in advanced ovarian adenocarcinoma, and uterine mixed mesodermal sarcoma; it may have limited activity treating cervical adenocarcinomas. It is inactive as first- or second-line therapy for uterine leiomyosarcomas, and seems inactive as first- or second-line therapy in endometrial and vulvar carcinomas.

REPORT DATE: 04/15/93 WORK UNIT # 4187

DETAIL SUMMARY SHEET

TITLE: GOG 26N: A Phase II Trial of Dihydroxyanthracenedione (DHAD) in Patients with Advanced Pelvic Malignancies

KEYWORDS: dihydroxyanthracenedione, pelvic malignancies

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Apr 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of dihydroxyanthracenedione (DHAD) in treating patients with advanced pelvic malignancies.

TECHNICAL APPROACH
Patients with histologically-confirmed advanced, recurrent, persistent, metastatic, or local gynecologic cancer with documented disease progression are eligible.

PRIOR AND CURRENT PROGRESS
A total of 191 patients have been entered from the entire GOG; 1 from WRAMC. No new patients have been enrolled this past year. It is currently closed to squamous and non-squamous cancer of the cervix, cancer of the vulva and vagina, epithelial ovarian carcinoma, adenocarcinoma and adenosquamous carcinoma of the uterus, and leiomyosarcomas and mixed mesodermal tumors of the uterus. There has been only one grade 4 hematologic toxicity.

CONCLUSIONS
The data includes minimal activity with DHAD in patients with ovarian cancer who have previously received doxorubicin. In patients with previously treated advanced carcinoma of the cervix, this drug also shows minimal activity. Patients with non-squamous carcinoma of the cervix, endometrium, vulva, and vagina, and uterine sarcomas, likewise have minimal response to DHAD.

REPORT DATE: 01/22/93 WORK UNIT # 4203

DETAIL SUMMARY SHEET

TITLE: GOG 26Q: A Phase II Trial of Aminothiadiazole in Patients with Advanced Pelvic Malignancies

KEYWORDS: aminothiadiazole, pelvic malignancies

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jan 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of aminothiadiazole in treating advanced pelvic malignancies (a Phase II trial).

TECHNICAL APPROACH
Aminothiadiazole (A-TD) will be administered at a dose of 125 mg/m2 IV per week. All patients will continue to receive A-TD until progression of disease is documented or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
There has been a total of 159 patients accrued by the GOG; 8 have been accrued this past year. One patient has been entered by Walter Reed. The protocol currently is closed for epithelial ovarian cancer, squamous cell cancer of the cervix, non-squamous cell cancer of the cervix, endometrial adenocarcinoma, leiomyosarcomas, and mixed mesodermal tumors of the uterus. There have been two grade 4 hematologic toxicities reported.

CONCLUSIONS
Aminothiadiazole used in this dose and schedule has minimal activity in previously treated patients with ovarian carcinoma and squamous cell carcinoma of the cervix, non-squamous cell carcinoma of the cervix, and endometrial adenocarcinoma.

REPORT DATE: 06/01/93 WORK UNIT # 4212

DETAIL SUMMARY SHEET

TITLE: GOG 72: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and a Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease

KEYWORDS: ovary, malignant, potential

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: May 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the biologic behavior of ovarian tumors of low malignant potential; to evaluate the effectiveness of chemotherapy against this disease (initially a Phase II study of melphalan); and to evaluate the response rate to cisplatin in melphalan failures.

TECHNICAL APPROACH

All patients with ovarian tumors considered to have a pathologic classification of low malignancy potential by a study reference pathologist will be eligible. Patients must have undergone adequate surgical staging procedures. Patients may have any stage of disease (from I-IV).

PRIOR AND CURRENT PROGRESS

There have been 477 patients entered into this study; 417 of whom are evaluable. Walter Reed has entered 26 patients. No significant toxicities have been reported among the patients treated. This protocol was closed to patient entry in March 1992.

CONCLUSIONS

Too early.

REPORT DATE: 07/21/93 WORK UNIT # 4225

DETAIL SUMMARY SHEET

TITLE: GOG 71: Treatment of Patients with Suboptimal (Bulky) Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radiation Therapy Vs. Radiation Therapy plus Adjuvant Extrafascial Hysterectomy, Phase III

KEYWORDS: suboptimal, carcinoma, cervix

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jul 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the role of adjunctive extrafascial hysterectomy in the treatment of suboptimal Stage I-B carcinoma of the cervix with negative para-aortic and high common iliac nodes. Evaluation of the survival and pattern of failure in suboptimal Stage I-B cancer.

TECHNICAL APPROACH

Patients with untreated, histologically confirmed Stage I-B barrel carcinoma of the cervix will undergo evaluation of para-aortic or high common iliac nodes by CT, lymphangiogram, or sonogram. If the nodes are suspicious or positive, they will be evaluated by surgery or fine needle aspiration. If surgically or cytologically negative or negative by extrinsic evaluation, the patient will be randomized to receive radiation alone or radiation followed by extrafascial hysterectomy.

PRIOR AND CURRENT PROGRESS

To date, 282 patients have been entered into this protocol by the entire GOG; Walter Reed has entered 10 patients. There have been five grade 4 gastrointestinal toxicities. Of the other four grade 4 toxicities, one was urinary, one was neurologic, and two were cardiovascular. This protocol was closed to patient entry in November 1991. Two patients are currently being followed on this protocol.

CONCLUSIONS

Too early.

REPORT DATE: 04/14/93 WORK UNIT # 4229

DETAIL SUMMARY SHEET

TITLE: GOG 86A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Carcinoma of the Endometrium

KEYWORDS: advanced, carcinoma, endometrium

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This study seeks to identify additional active agents for treating advanced or recurrent endometrial adenocarcinoma by studying single new drugs in patients with this disease who have not been previously exposed to chemotherapy.

TECHNICAL APPROACH
Patients must have histologically confirmed advanced, persistent, or recurrent endometrial carcinoma with documented disease progression after local therapy. All patients must have measurable disease. Patients must have failed local therapeutic measures or must be considered incurable with local therapy.

PRIOR AND CURRENT PROGRESS
GOG #86 is a master protocol. Please see the individual protocols for further information.

CONCLUSIONS
See individual protocols for further information.

REPORT DATE: 05/28/93 WORK UNIT # 4231

DETAIL SUMMARY SHEET

TITLE: GOG 87A: Master Protocol for Phase II Drug Studies in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: advanced, uterus, sarcoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To allow the best possible chance for a new cytotoxic agent to demonstrate activity, this study constitutes a Phase II design in a population of patients who have had no prior drug therapy.

TECHNICAL APPROACH

To treat an average sample size of 30 patients per drug studied for each of the following cell categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. Patients will have histologically confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive a chemotherapeutic regimen as outlined in each segment of the protocol.

PRIOR AND CURRENT PROGRESS

Groupwide there have been 92 patients entered into GOG 87-B (6 from WRAMC), and 79 (1 from WRAMC) patients have been entered into GOG 87-C. Grade 4 adverse effects for 87-B include one thrombocytopenia, six granulocytopenias, two neurotoxicities, nine leukopenias, and one anemia. There has been one death related to therapy. The grade 4 adverse effects for 87-C include two leukopenias and six neutropenias. Protocol 87-B was closed for mixed mesodermal tumors in March 1988 and for leiomyosarcomas in June 1989. Protocol 87-C was closed for mixed mesodermal tumors in July 1989 and for leiomyosarcomas in May 1991.

CONCLUSIONS

See individual protocols.

REPORT DATE: 05/28/93 WORK UNIT # 4232

DETAIL SUMMARY SHEET

TITLE: GOG 87B: A Phase II Trial of Ifosfamide and the Uroprotector, Mesna, in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: ifosfamide, Mesna, sarcoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This study is designed to allow the best possible chance for a new cytotoxic agent to demonstrate activity, constituting a Phase II design in a population of patients who have had no prior drug therapy. The study design will involve treating an average sample size of 30 evaluable patients with ifosfamide for each of the following cell type categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas.

TECHNICAL APPROACH
Patients will have histologically confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive ifosfamide and Mesna for five days every 4 weeks until disease progression or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
There have been 92 patients entered into this protocol for the entire GOG; (none during this past year); 86 of whom are evaluable. WRAMC has entered six patients (none this past year). GOG reports grade 4 toxicities as follows: nine leukopenia, one thrombocytopenia, six granulocytopenia, two neurotoxic, and one anemia.

CONCLUSIONS
Ifosfamide/Mesna may be the most active single agent therapy for advanced mixed mesodermal tumors of the uterus.

REPORT DATE: 08/19/93 WORK UNIT # 4234

DETAIL SUMMARY SHEET

TITLE: GOG 26U: A Phase II Trial of Ifosfamide and the Uroprotector, Mesna, in Patients with Advanced Pelvic Malignancies

KEYWORDS: ifosfamide, Mesna, malignancy

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Aug 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to higher priority methods of treatment. A "rejection"-type design will be used involving a fixed sample size of 25 patients per disease site per drug or combination of drugs studied.

TECHNICAL APPROACH
Ifosfamide, like cyclophosphamide, requires activation by a hepatic microsomal NADPH-dependent mixed-function oxidase system. A bi-ability to crosslink and fragment DNA is produced. Mesna has been shown to acceptably reduce the urothelial toxicity of ifosfamide in several European studies. All patients must have biopsy proven advanced pelvic malignancy to be eligible.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 219 patients into this study; Walter Reed has entered 5 patients. There have been 13 grade 4 toxicities for ovarian sarcoma: 5 leukopenia, 5 granulocytopenia, 1 thrombocytopenia, 1 renal, and 1 anemia. For nonsquamous cell carcinoma there have been 9 grade 4 toxicities: 1 thrombocytopenia, 6 granulocytopenia, 1 GU, and 1 alopenia. For carcinoma of the endometrium, there have been 16 grade 4 toxicities: 4 thrombocytopenias, 10 granulocytopenias, 1 neurotoxicity, and 1 bronchospasm.

CONCLUSIONS
Ifosfamide is an active Phase II drug in relapsed epithelial ovarian carcinoma, although neurotoxicity is a limiting factor in this patient population. Ifosfamide possesses minimal activity in previously treated squamous cell carcinoma of the cervix.

REPORT DATE: 03/13/93 WORK UNIT # 4244

DETAIL SUMMARY SHEET

TITLE: GOG 90: Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors, Phase II

KEYWORDS: ovarian, germ cell, tumors

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Mar 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP), followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors.

TECHNICAL APPROACH

Eligible patients include those with histologically confirmed malignant germ cell tumors of the ovary who have incompletely resected Stage II, III, or IV disease. Patients who have previously received pelvic radiation therapy will be eligible, but the initial dose of etoposide will be reduced 20%.

PRIOR AND CURRENT PROGRESS

To date, 75 patients have been entered into this protocol by all GOG member institutions; 8 this past year. Walter Reed has entered no patients. There have been 43 grade 4 episodes of granulocytopenia, 25 episodes of grade 4 leukopenia, 6 episodes of thrombocytopenia, 3 episodes of grade 4 GI reactions, 1 dermatologic grade 4 reaction, and 1 grade 4 allergic reaction.

CONCLUSIONS

Too early.

REPORT DATE: 06/11/93 WORK UNIT # 4247

DETAIL SUMMARY SHEET

TITLE: GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected Stage IAi and IBi and IAii and IBii Ovarian Cancer, Phase III

KEYWORDS: randomized, ovarian, cancer

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: May 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

This study seeks to compare the progression-free interval and overall survival between P32 and a combination of cyclophosphamide and cisplatin for patients with early ovarian cancer and to determine the patterns of relapse for each form of therapy.

TECHNICAL APPROACH

All patients must have a histopathologic diagnosis of epithelial ovarian cancer of each histologic cell type: serous mucinous; others include endometrioid, transitional mesonephroid (clear cell), adenocarcinoma (endometrioid with squamous metaplasia), mixed epithelial, and unclassifiable (undifferentiated).

PRIOR AND CURRENT PROGRESS

As of July 1993, the entire GOG has entered 223 patients (43 since July 1992); 182 are currently evaluable. Since the protocol began, WRAMC and its affiliate institutions have entered 15 patients (5 during the past year); 5 have been treated at WRAMC (1 during the past year). WRAMC patients (four on P32 and one on chemotherapy) have experienced no adverse reactions, serious toxicity, or deaths. As of July 1993, the GOG has administered over 364 treatment cycles (P32 and chemotherapy combined) which have resulted in 45 grade 4 neutropenic episodes, 3 grade 4 thrombocytopenias, and 1 grade 4 GI toxicity. Two patients experienced small bowel perforation during P32 administration. There have been no treatment related deaths. This protocol remains open for patient accrual.

CONCLUSIONS

Too early.

REPORT DATE: 06/17/93 WORK UNIT # 4251

DETAIL SUMMARY SHEET

TITLE: GOG 26W: A Phase II Trial of Echinomycin in Patients with Advanced Pelvic Malignancies

KEYWORDS: echinomycin, pelvic malignancies

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of echinomycin in the treatment of advanced or recurrent pelvic malignancies.

TECHNICAL APPROACH
Eligible patients include those who have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
To date, the entire GOG has entered 101 patients into this study (none this past year). Walter Reed has entered four patients. There has been one grade 4 GI adverse effect reported. This study has been closed to patient accrual since November 1992.

CONCLUSIONS
Echinomycin displays minimal activity in patients with squamous cell carcinoma of the cervix, and nonsquamous carcinoma of the cervix, and in patients with ovarian epithelial carcinoma, nonsquamous carcinoma of the cervix, and carcinoma of the endometrium who have had prior chemotherapy.

REPORT DATE: 07/21/93 WORK UNIT # 4254

DETAIL SUMMARY SHEET

TITLE: GOG 93: Evaluation of Intraperitoneal Chromic Phosphate Suspension Therapy Following Negative Second-Look Laparotomy for Epithelial Ovarian Carcinoma, Stage III, Phase III

KEYWORDS: chromic phosphate, ovarian, carcinoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MC

DEPARTMENT: Depar ent of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jul 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the role of intraperitoneal chromic phosphate suspension therapy in patients with Stage III epithelial ovarian carcinoma who have no detectable evidence of disease at the second-look laparotomy.

TECHNICAL APPROACH

To be eligible, patients must have histologically confirmed primary epithelial carcinoma of the ovary and be in complete clinical remission. Patients must have a diagnosis of FIGO Stage III ovarian carcinoma.

PRIOR AND CURRENT PROGRESS

Altogether, the entire GOG has entered 116 patients into this study; 53 during this past year. WRAMC has enrolled one patient altogether. This patient was enrolled during the past year. There has been one grade 4 (hematologic, GI, and surgical) adverse effect from the entire GOG experience with this protocol.

CONCLUSIONS

Too early.

REPORT DATE: 09/16/93 WORK UNIT # 4255

DETAIL SUMMARY SHEET

TITLE: GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin and Cisplatin Therapy in Totally Reducing Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements, Phase II

KEYWORDS: VP-16, bleomycin, cisplatin

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effect of adjuvant VP-16, bleomycin, and cisplatin chemotherapy in patients with endodermal sinus tumor, choriocarcinoma, embryonal carcinoma, and grade 2 and 3 immature teratoma of the ovary after removal of all gross tumors.

TECHNICAL APPROACH
Eligible patients include those with histologically confirmed Stage I choriocarcinoma, endodermal sinus tumor, embryonal carcinoma, and grade 2 and 3 immature teratoma. Patients with Stage II and III disease are also eligible if all gross tumor is removed. Serum AFP and beta-HCG levels should be normal.

PRIOR AND CURRENT PROGRESS
To date, 117 patients have been entered into this study (none this past year); Walter Reed has entered 2 patients. Reported toxicities are as follows: 9 grade 4 leukopenia, 2 grade 4 GI, 1 grade 4 dermatologic, 3 grade 4 thrombocytopenia, and 41 grade 4 granulocytopenia. This protocol was closed to patient entry in February 1992, but two patients are still being followed.

CONCLUSIONS
Too early for analysis.

REPORT DATE: 10/19/92 WORK UNIT # 4257

DETAIL SUMMARY SHEET

TITLE: GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

KEYWORDS: radiation, endometrial, adenocarcinoma

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if patients with intermediate risk endometrial adenocarcinoma who have no spread of disease to their lymph nodes benefit from postoperative pelvic radiotherapy. To evaluate how the addition of pelvic radiotherapy will alter the site and rate of cancer recurrence in these intermediate risk patients.

TECHNICAL APPROACH

Patients with primary histologically confirmed grades 2 and 3 endometrial adenocarcinoma are eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, pelvic washings, and found to be surgical Stage I. Patients must have myometrial invasion.

PRIOR AND CURRENT PROGRESS

There have been 245 patients entered on this protocol through the entire GOG (42 during the past year). Walter Reed has entered 15 patients altogether (2 during the past year). There has been one GI grade 4 toxicity, one cutaneous grade 4 toxicity, and one grade 4 obstruction toxicity.

CONCLUSIONS

Too early.

REPORT DATE: 06/17/93 WORK UNIT # 4263

DETAIL SUMMARY SHEET

TITLE: GOG 26X: A Phase II Trial of Gallium Nitrate in Patients with Advanced Pelvic Malignancies

KEYWORDS: gallium nitrate, pelvic malignancies

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR NC
ASSOCIATES: Park, Robert MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of gallium nitrate in the treatment of advanced or recurrent gynecologic cancers.

TECHNICAL APPROACH
Patients will have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy of established treatments.

PRIOR AND CURRENT PROGRESS
To date, 50 patients have been entered into this protocol from the entire GOG; 6 during the past year. No patients have been entered from WRAMC. No grade 4 adverse effects have been reported. This study has been closed to patient accrual as of 8 Jan 93.

CONCLUSIONS
Gallium nitrate has modest activity in previously treated patients with epithelial ovarian carcinoma.

REPORT DATE: 06/17/93 WORK UNIT # 4265

DETAIL SUMMARY SHEET

TITLE: GOG 102 A (Master Protocol): Intraperitoneal Administration of Cisplatin and 5-FU in Residual Ovarian Carcinoma, Phase II

KEYWORDS: cisplatin, 5-fluorouracil, ovarian carcinoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 238 Total: $ 238

STUDY OBJECTIVE
To determine the activity of cisplatin and 5-fluorouracil when used by the intraperitoneal route in patients who have persistent minimal residual disease epithelial ovarian malignancies after standard therapy.

TECHNICAL APPROACH
Patients with primary, histologically documented, epithelial carcinoma of the ovary, and patients who have had partial or incomplete responses to combination chemotherapy and who have documented minimal residual disease (1.0 cm or less maxi tumor diameter) at second look laparotomy following chemotherapy are enrolled. Patients with a history of complete response followed by a recurrence with no residual nodule greater than 1 cm in diameter are also eligible.

PRIOR AND CURRENT PROGRESS
There have been 48 patients entered into this protocol for the entire GOG (none during the past year). No WRAMC patients have been entered from Walter Reed. There has been one grade 4 leukopenia, four grade 4 neutropenias, one grade 4 anemia, and one grade 4 hepatic toxicity. GOG 102B was closed to new patient entry in December 1988; however, the Master Protocol 102-A remains in effect.

CONCLUSIONS
This is an active salvage regimen in small volume, cisplatin-sensitive tumors.

REPORT DATE: 07/21/93 WORK UNIT # 4266

DETAIL SUMMARY SHEET

TITLE: GOG 76A: Master Protocol for Phase II Drug Studies in the Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix.

KEYWORDS: advanced, squamous cell carcinoma, cervix

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To continue identification of new active drugs in the treatment of advanced or recurrent squamous cell carcinomas of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

TECHNICAL APPROACH
Patients enrolled in individual protocols under this Master Protocol will have histologically confirmed advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy.

PRIOR AND CURRENT PROGRESS
GOG 76-A is a Master Protocol. Walter Reed has two 76 protocols approved: 76-I and 76-S. The entire GOG has entered 394 patients into 76-I, of which 3 have been from Walter Reed. The GOG has entered 32 patients into 76-S, of which Walter Reed has entered none. There have been approximately 40 grade 4 toxicities; 21 leukopenias, 10 neutropenias, 1 cutaneous, 2 neurotoxicities, 1 fever, 4 thrombocytopenias, and 1 hypocalcemia. Both protocols have been closed to patient accrual (76-I in February 1990 and 76-S in May 1990).

CONCLUSIONS
See individual protocols.

REPORT DATE: 11/15/93 WORK UNIT # 4268

DETAIL SUMMARY SHEET

TITLE: GOG 26DD: A Phase II Trial of Amonafide in Patients with Advanced Pelvic Malignancies

KEYWORDS: amonafide, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of amonafide in the treatment of advanced pelvic malignancies.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
There have been 51 patients entered into this protocol from the entire GOG (none during the past year). Walter Reed has entered three patients; none since the FY-91 report. There have been 19 grade 4 hematologic toxicities, 1 grade 4 GI toxicity, and 1 grade 4 renal toxicity reported. No treatment deaths have been reported. The protocol is closed to patient accrual and is open for follow-up only.

CONCLUSIONS
Although amonaride has slight activity in epithelial tumors of the ovary and squamous cell cancer of the cervix, further studies in these tumor types are not warranted due to both low activity and severe hematologic toxicity.

REPORT DATE: 01/11/93 WORK UNIT # 4274

DETAIL SUMMARY SHEET

TITLE: GOG 104: Intraperitoneal Cisplatinum/Intravenous Cyclophosphamide Vs. Intravenous Cisplatinum/Intravenous Cyclophosphamide in Patients with Nonmeasurable Disease Stage III Ovarian Cancer, Phase III

KEYWORDS: cis-platinum, cyclophosphamide, ovary

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To carry out a Phase III randomized trial of intermediate dose intraperitoneal cis-platinum plus intravenous cyclophosphamide versus intermediate dose intravenous cis-platinum plus intravenous cyclophosphamide for optimal Stage III ovarian cancer.

TECHNICAL APPROACH

Patients will be randomized to receive one of the two regimens listed above. Eligible patients must have a histologically confirmed pure epithelial ovarian carcinoma. Those with a borderline tumor will be excluded.

PRIOR AND CURRENT PROGRESS

To date, the entire GOG has entered 292 patients; 34 this past year. Nine patients have been entered from WRAMC; two during this reporting year. There have been 39 grade 4 neutropenia episodes and 8 grade 4 thrombocytopenic episodes reported. There have been 3 grade 4 GU toxicities and 8 grade 4 GI toxicities. There have been no reported deaths.

CONCLUSIONS

Too early.

REPORT DATE: 03/29/93 WORK UNIT # 4275

DETAIL SUMMARY SHEET

TITLE: GOG 107 A Randomized Study of Doxorubicin Vs. Doxorubicin Plus Cisplatin in Patients with Primary Stage III and IV Recurrent Endometrial Adenocarcinoma, Phase III

KEYWORDS: doxorubicin, cisplatin, endometrial

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
The major objective of this study is to determine whether the addition of cisplatin to doxorubicin offers significant improvement in the frequency of objective response, the duration of progression free interval, and the length of survival as compared to doxorubicin alone.

TECHNICAL APPROACH
Eligible patients must have Stage III, Stage IV, or recurrent endometrial carcinoma. Patients must have measurable disease. Patients may have received prior hormonal therapy or therapy with biologic response modifiers.

PRIOR AND CURRENT PROGRESS
To date, 299 patients have been enrolled by the entire GOG (158 during the past year). One patient has been entered from Walter Reed during the past year (the only WRAMC patient). There have been 37 grade 4 granulocytopenic toxicities, 4 rade 4 thrombocytopenic toxicities, 3 grade 4 anemias, and 4 grade 4 GI toxicities. The protocol closed for patient entry on 1 Dec 92.

CONCLUSIONS
Too early.

REPORT DATE: 06/11/93 WORK UNIT # 4277

DETAIL SUMMARY SHEET

TITLE: GOG 108: Ifosfamide and the Uroprotector, Mesna, with or without Cisplatin in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus, Phase III

KEYWORDS: ifosfamide, uterine, sarcoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To confirm reported high response rates of advanced or recurrent mixed mesodermal tumors of the uterus to ifosfamide/Mesna. To determine whether the addition of cisplatin to ifosfamide/Mesna improves response rates or survival in patients with these tumors.

TECHNICAL APPROACH
Eligible patients include those with primary, histologically confirmed, heterologous or homologous (carcinosarcoma) mixed mesodermal tumors of the uterus. All patients must have measurable disease. Patients who have received prior chemotherapy are not eligible.

PRIOR AND CURRENT PROGRESS
As of July 1993, the entire GOG has entered 121 patients (50 since the last report); 82 are currently evaluable. WRAMC has entered two patients since the protocol began (both during the past year). One patient experienced disease progression and died of disease. There were no treatment related complications. The other patients completed therapy with one episode of grade 4 hematologic toxicity (neutropenia) out of eight total chemotherapy treatments. There were no lasting sequelae. As of July 1993, the entire GOG had administered over 600 treatment cycles; there were 36 grade 4 neutropenic episodes, 11 grade 4 thrombocytopenias, and 2 grade 4 GI toxicities (nausea and vomiting). There have been no treatment related deaths. This protocol remains open for patient accrual.

CONCLUSIONS
Too early.

REPORT DATE: 07/21/93 WORK UNIT # 4278

DETAIL SUMMARY SHEET

TITLE: GOG 26EE A Phase II Trial of Didemnin B in Patients with Advanced Pelvic Malignancies

KEYWORDS: Didemnin B, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of Didemnin B in the treatment of advanced or recurrent pelvic carcinomas.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
To date, 43 patients have been entered into this study by the entire GOG (none during the past year). Walter Reed has entered no patients. One grade 4 gastrointestinal toxicity has been reported. The protocol has been closed to squamous cervical and epithelial ovarian cancer patients and was terminated as of November 1992.

CONCLUSIONS
Didemnin B is ineffective with the schedules utilized.

REPORT DATE: 01/11/93 WORK UNIT # 4281

DETAIL SUMMARY SHEET

TITLE: GOG 8801 A Phase I Evaluation of Multiple Daily Fraction Radiation and Hydroxyurea in Patients with Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, hydroxyurea, cervix

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus hydroxyurea in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with hydroxyurea and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix; squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIA, IIIB, or IV disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

To date, 36 patients have been accrued by the entire GOG; 2 during the past year. Walter Reed has entered 5 patients; none during this reporting period. No toxicity reports are available at this time.

CONCLUSIONS

Too early.

REPORT DATE: 01/21/93 WORK UNIT # 4282

DETAIL SUMMARY SHEET

TITLE: GOG 8901 A Phase I Evaluation of Multiple Daily Fraction Radiation and 5FU Plus Cisplatin in Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, 5FU, cisplatin

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus 5-fluorouracil (5-FU) and cisplatin in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with 5-FU, cisplatin, and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIB, or IVA disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

To date, 34 patients have been accrued by the entire GOG; 14 during this reporting period. Walter Reed has entered nine patients altogether; four during this reporting period. No toxicity reports are available at this time.

CONCLUSIONS

Too early.

REPORT DATE: 06/01/93 WORK UNIT # 4291

DETAIL SUMMARY SHEET

TITLE: GOG 26GG A Phase II Trial of Fazarabine in Patients with Advanced or Recurrent Pelvic Malignancies

KEYWORDS: Fazarabine, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of Fazarabine in the treatment of advanced or recurrent gynecologic cancers refractory to curative therapy or established treatments.

TECHNICAL APPROACH
Patients with histologically confirmed gynecologic cancer either recurrent or advanced on initial presentation and refractory to curative therapy or established treatments will be eligible. The patients will be treated with Fazarabine at the dosage of 30 mg/m2/day for 5 days. Cycles of therapy will be repeated every 28 days.

PRIOR AND CURRENT PROGRESS
To date, 45 patients have been accrued by the entire GOG (one during the past year). Walter Reed has entered one patient (none during the past year). Four cases of grade 4 neutropenia (two grade 4 leukopenias and one grade 4 sepsis) have been reported. No treatment related deaths have been reported. This protocol was closed to squamous cell carcinoma of the cervix in June 1990 and to epithelial cell carcinoma of the ovary in September 1990.

CONCLUSIONS
Fazarabine exhibits no significant activity in patients with epithelial tumors of the ovary and squamous cell carcinoma of the cervix at the dose and schedule tested.

REPORT DATE: 06/16/93 WORK UNIT # 4294

DETAIL SUMMARY SHEET

TITLE: COG 8803 Flow Cytometrically Determined Tumor DNA Content in Advanced Epithelial Ovarian Cancer

KEYWORDS: flow cytometry, DNA, ovarian carcinoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if tumor ploidy and cell proliferation can be correlated to various tumor and host factors, tumor responses, second look laparotomy findings, relapse and patient survival. To determine if tumor ploidy and cell proliferation are consistent between primary and metastatic sites and if they remain stable before and after chemotherapy.

TECHNICAL APPROACH
Patients with advanced (Stage III or IV) epithelial ovarian cancer that were previously entered on GOG Protocols 47, 52, or 60 will be eligible. In addition, patients must have received enough chemotherapy on protocol to be evaluable for response, have a paraffin-embedded ovarian tumor specimen from the pretreatment laparotomy available for use, and have adequate follow-up information available to include second-look laparotomy findings.

PRIOR AND CURRENT PROGRESS
To date, 274 patients have been entered for the entire GOG (none this past year). No patients from Walter Reed have been entered.

CONCLUSIONS
Too early.

REPORT DATE: 06/16/93 WORK UNIT # 4295

DETAIL SUMMARY SHEET

TITLE: GOG 8809 Flow Cytometrically Determined Tumor DNA Content in Ovarian Tumors of Low Malignant Potential

KEYWORDS: flow cytometry, DNA, ovarian tumors

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the DNA content of borderline ovarian tumors can be correlated with extent/stage of the tumor, potential for recurrence, and patient survival.

TECHNICAL APPROACH
Patients previously entered on GOG Protocol 72 with all stages of ovarian tumors of low malignant potential (any histologic type) can be entered. In addition, one paraffin-embedded specimen from pretreatment laparotomy and adequate follow-up information, to include second-look laparotomy findings or time to progression, must be available.

PRIOR AND CURRENT PROGRESS
To date, 151 patients have been entered for the entire GOG (43 during the past year). Five patients have been entered from Walter Reed (three during the past year). This protocol was closed to patient entry in February 1993.

CONCLUSIONS
Too early.

REPORT DATE: 06/16/93 WORK UNIT # 4296

DETAIL SUMMARY SHEET

TITLE: GOG 8810 Flow Cytometrically Determined DNA Content in Endometrial Carcinoma

KEYWORDS: flow cytometry, DNA, adenocarcinoma

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the DNA content of primary, recurrent and metastatic endometrial adenocarcinoma, and to identify whether the presence of aneuploid cell populations is related to histologic cell type, or grade or stage of the tumor, lymph node or distant metastasis, progression free interval, or survival. To determine whether tumor ploidy is consistent between primary tumors and their metastasis.

TECHNICAL APPROACH

Patients are eligible if previously entered on GOG Protocol 33, and if a paraffin block sample from the D&C or hysterectomy is available. If metastatic tumor is present, one paraffin block of the metastatic tumor would be highly desirable.

PRIOR AND CURRENT PROGRESS

To date, 293 patients have been entered for the entire GOG; 5 patients have been entered by Walter Reed. The protocol was closed to patient entry in November 1991. Four patients are being followed on this study.

CONCLUSIONS

Too early.

REPORT DATE: 06/16/93 WORK UNIT # 4298

DETAIL SUMMARY SHEET

TITLE: GOG 111 A Phase III Randomized Study of Cyclophosphamide and Cisplatin Vs. Taxol and Cisplatin in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma

KEYWORDS: ovarian carcinoma, cisplatin, Taxol

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine rate, response duration, and survival in suboptimal Stage III and Stage IV ovarian cancer treated with two different platinum-based combination chemotherapy regimens. To compare the relative toxicities of the two regimens.

TECHNICAL APPROACH
Patients with established ovarian epithelial cancer, suboptimal (1 cm in diameter) Stage III or Stage IV, are eligible. All patients must have optimal surgery for ovarian cancer. The following histologically confirmed ovarian malignancies are eligible: serous adenocarcinoma, mucinous adenocarcinoma, clear-cell adenocarcinoma, endometrioid adenocarcinoma, undifferentiated carcinoma, and mixed epithelial carcinoma.

PRIOR AND CURRENT PROGRESS
There have been a total of 394 patients entered into this protocol for the entire GOG. Eleven patients have been entered from Walter Reed. There have been 266 grade 4 leukopenias, 1 grade 4 anemia, 4 grade 4 thrombocytopenias, 12 grade 4 GI adverse effects, 1 grade 4 cardiac toxicity, 1 grade 4 renal toxicity, and 1 grade 4 neurologic toxicity. This protocol was closed to patient entry in March 1992. One patient is being followed.

CONCLUSIONS
Too early.

REPORT DATE: 10/18/92 WORK UNIT # 4302

DETAIL SUMMARY SHEET

TITLE: GOG 8906 Extended Radiation Therapy With Concomitant 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes

KEYWORDS: radiation, cervix, para-aortic

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess tolerance dose levels of 5-FU infusion and cisplatin chemotherapy in a prospective, dose escalating fashion with respect to acute toxicity when administered concomitantly with pelvic-para-aortic field radiation therapy. To assess long-term treatment toxicities.

TECHNICAL APPROACH
All patients have primary, previously untreated, histologically confirmed, invasive carcinoma of the uterine cervix (squamous, adenosquamous, and adenocarcinoma). All clinical stages, except clinical Stage IIIA and IVB, with metastasis to the para-aortic lymph nodes proven by cytologic or histologic means are eligible for this study.

PRIOR AND CURRENT PROGRESS
There have been 11 patients entered into this protocol through the entire GOG. No patients have been entered from WRAMC. There have been no documented grade 4 toxicities reported by the entire GOG.

CONCLUSIONS
Too early.

REPORT DATE: 11/15/92 WORK UNIT # 4303

DETAIL SUMMARY SHEET

TITLE: GOG 26-11 Phase II Trial of 5-Fluorouracil and High Dose Leucovorin in Advanced or Recurrent Pelvic Malignancies

KEYWORDS: pelvic, malignancies, 5-FU/leucovorin

PRINCIPAL INVESTIGATOR: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of leucovorin in advanced metastatic or recurrent pelvic carcinomas.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed recurrent or metastastic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
There have been 106 patients entered onto this protocol from the entire GOG; WRAMC has entered one. There have been 14 grade 4 hematologic toxicities (1 thrombocytopenia, 13 granulocytopenias) and 2 grade 4 GI toxicities. The protocol is closed to squamous cell cancer of the cervix and epithelial cancer of the ovary.

CONCLUSIONS
Too early.

REPORT DATE: 03/30/93 WORK UNIT # 4305

DETAIL SUMMARY SHEET

TITLE: GOG 101 A Phase II Evaluation of Preoperative Chemoradiation for Advanced Vulvar Cancer

KEYWORDS: vulva, cancer, chemoradiation

PRINCIPAL INVESTIGATOR: Mayer, Allan LTC(P) MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the feasibility, effectiveness, and morbidity of using preoperative chemoradiation and surgery in advanced cancer of the vulva.

TECHNICAL APPROACH
Depending on the TNM stage, patients will be treated with split course chemotherapy followed by radiation therapy to the primary lesion and/or pelvic and groin nodes. All patients will then undergo surgical resection of the residual tumor.

PRIOR AND CURRENT PROGRESS
To date, 83 patients have been enrolled groupwide in the GOG. Walter Reed has entered no patients. There has been no report on the incidence of serious or unexpected adverse reactions by the GOG coordinators.

CONCLUSIONS
Too early to determine.

REPORT DATE: 06/01/93 WORK UNIT # 4308

DETAIL SUMMARY SHEET

TITLE: GOG 125: Extended Field Radiation Therapy with Concomitants 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes

KEYWORDS: radiation, cervical, lymph nodes

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Patients with cervical carcinoma and para-aortic lymph node metastasis will receive extended field radiation and concomitant chemotherapy with 5-FU and cisplatin. The study will assess progression-free survival, overall survival, sites of failure, and morbidity.

TECHNICAL APPROACH
All patients with primary, previously untreated, histologically confirmed invasive carcinoma of the cervix will be eligible. Any clinical stage (except IIIA and IVB) are eligible. Metastasis to para-arotic nodes must be proven histologically or cytologically. Patients will receive pelvic and para-aortic radiation and cisplatin 50 mg/m2 on days 1 and 29, and 5-FU 1000 mg/m2 on days 2, 3, 4, 5 and 30, 31, 32, 33.

PRIOR AND CURRENT PROGRESS
To date, 42 patients have been accrued in the entire GOG. Walter Reed has entered one patient. One case of grade 4 GI toxicity has been reported.

CONCLUSIONS
Too early.

REPORT DATE: 06/22/93 WORK UNIT # 4309

DETAIL SUMMARY SHEET

TITLE: GOG 102: A Randomized Comparison of hydroxyurea vs. Hydroxyurea, 5-FU Infusion and Cisplatin vs. Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages II-B, III, or IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

KEYWORDS: cervix, carcinoma, Phase III

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether hydroxyurea; hydroxyurea, 5-FU infusion plus bolus cisplatin; or weekly cisplatin is superior as a potentiator of radiation therapy in locally advanced cervical carcinoma.

TECHNICAL APPROACH
Patients with cervical carcinoma (Stages IIB, IIA, IIIB, or IVA) will undergo extraperitoneal staging surgery. Those patients with negative para-aortic nodes will then be randomized to receive radiotherapy plus either: 1) cisplatin; 2) cisplatin, 5-FU and hydroxyurea; or 3) hydroxyurea. Following the completion of therapy the patients will be followed clinically.

PRIOR AND CURRENT PROGRESS
To date, the entire GOG has enrolled 57 patients. Walter Reed has enrolled one patient. Three patients on this study have experienced grade 3 hematologic toxicity. There have been no deaths during treatment.

CONCLUSIONS
Too early.

REPORT DATE: 08/19/93 WORK UNIT # 4310

DETAIL SUMMARY SHEET

TITLE: GOG: 136 Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying the Causes, Diagnosis, Prevention and Treatment of Cancer

KEYWORDS: ovarian, tissue, collection

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions, and to provide a long-term storage repository for ovarian tumors and serum. The material will be used in studies to better understand the molecular biology of ovarian tumors.

TECHNICAL APPROACH

All patients who have had ovarian tumor tissue or extra-ovarian peritoneal serous carcinoma tissue removed are eligible. All patients who have had ovaries removed because of a family history of ovarian cancer are eligible. The tissue, when removed, is shipped along with serum specimens to the GOG repository facility.

PRIOR AND CURRENT PROGRESS

To date, Walter Reed has entered 11 patients into this protocol. There have been 311 entries from the entire GOG. No unexpected or serious adverse reactions have been reported.

CONCLUSIONS

Too early.

REPORT DATE: 09/16/93 WORK UNIT # 4311

DETAIL SUMMARY SHEET

TITLE: GOG 134: A Phase III Trial of Taxol at Thrfee Dose Levels and G-CSFF at Two Dose Levels in Platinyum-Resistant Ovarian Carcinoma

KEYWORDS: Taxol, ovarian, G-CSF

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC .

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if Taxol at different dose levels affects response rate, progression-free interval, or survival in patients with platinum-resistant ovarian cancer; to compare toxicities of the regimens; and to compare the efficacy and toxicity of G-CSF in patients receiving high dose Taxol.

TECHNICAL APPROACH
Patients with platinum-resistant ovarian epithelial cancer with clinically measurable disease will be randomized to receive Taxol at three different dose levels. Patients at the highest dose level will also receive G-CSF at one of two dose levels. Patients are then followed clinically to assess response.

PRIOR AND CURRENT PROGRESS
To date, the entire GOG has enrolled 182 patients, of which 97 are presently evaluable. Walter Reed has enrolled four patients. Of the 97 patients who are evaluable, 50 have died or experienced disease progression. Toxicities have included 59 grade 4 neutropenic episodes, 1 grade 4 GI toxicity, and 1 grade 4 neurologic toxicity. This protocol remains open for patient accrual.

CONCLUSIONS
Too early for conclusions.

REPORT DATE: 07/25/93 WORK UNIT # 4813

DETAIL SUMMARY SHEET

TITLE: Leishmania Survivability and Infectivity in Human Blood Products

KEYWORDS: leishmania, survival, blood

PRINCIPAL INVESTIGATOR: Daugirda, Joanne CPT MS

DEPARTMENT: Department of Pathology and Area Laboratories STATUS: Completed
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the survivability of viscerotropic Leishmania tropica in human whole blood and blood products maintained at blood bank storage conditions and temperatures. Also, to determine if infected units of blood can be prophylactically treated to kill or remove the parasite to render the blood useable.

TECHNICAL APPROACH
The parasite will be introduced into whole blood as either intramonocytic amastigotes or promastigotes. The blood will remain as whole or be divided into its cellular components. At intervels, the blood will be cultured to determine survivability of the parasite. Whole blood will be seeded with intra-monocytic amastigotes and treated with either gentian violet, filtration, or irradiation. Samples will be cultured to determine parasite survival.

PRIOR AND CURRENT PROGRESS
Leishmania tropica (viscerotropic strain WR1063) survived in whole blood for 15 days, packed RBC for 20 days, platelets for at least 5 days, and frozen RBC for at least 6 months when maintained at blood storage conditions. Prophylactic treatment with gentian violet and filtration rendered the infected units culture negative. There have been a total of 30 people enrolled in the study. None of the volunteers experienced adverse reactions from their donations.

CONCLUSIONS
The results indicate that a unit of blood infected with viscerotropic Leishmania tropica could cause transfusion transmitted leishmaniasis; however, prophylactic treatment of potentially infected units may provide safe, transfusable products.

REPORT DATE: 07/07/93 WORK UNIT # 4814

DETAIL SUMMARY SHEET

TITLE: A Comparison of Fresh and Rejuvenated Red Blood Cells Cryopreserved with Hydroxyethyl Starch (HES)

KEYWORDS: red blood cells, cryopreservation, hydroxyethyl starch

PRINCIPAL INVESTIGATOR: Welsh, Victoria CPT MS
ASSOCIATES: Supon, Patrick LTC MS

DEPARTMENT: Department of Pathology and Area Laboratories

STATUS: Completed
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 1,325 Previous FYs: $ 0 Total: $ 1,325

STUDY OBJECTIVE

To examine whether rejuvenated red blood cells (RBC) can be effectively frozen with the extracellular cryoprotectant, hydroxyethyl starch (HES), and to demonstrate similar RBC recovery and viability with fresh RBC frozen with the same cryoprotectant.

TECHNICAL APPROACH

The in vitro properties of expired human RBC (approximately 220 ml) that were rejuvenated and then frozen with HES were compared to those of fresh human RBC frozen with HES within 24 hours of collection. Post-thaw measurements of intracellular adenosine-5'-triphosphate (ATP) and 2,3-diphosphoglyceric acid (2,3-DPG) levels, saline stability, plasma stability, and RBC recovery were the primary response variables for this study.

PRIOR AND CURRENT PROGRESS

The principal investigator was trained at the British Army Blood Supply Depot (ABSD), United Kingdom, on the cryopreservation of RBC in the presence of HES. Equipment and materials provided by the ABSD were utilized. Ten volunteer subjects were recruited to donate blood (for a total of 20 units over a 2-month period) for use in this study, and no adverse reactions were noted. This research was conducted to complete a thesis and satisfy requirements for a Master's in Science degree offered in affiliation with the Tri-Service Blood Bank Fellowship at Walter Reed Army Medical Center.

CONCLUSIONS

The rejuvenated RBC appeared to survive the freeze-thaw process better than the fresh units, as demonstrated by the increase in ATP and the smaller loss of 2,3-DPG levels measured post-thaw. RBC recovery and saline stability assays were similar between the rejuvenated and fresh RBC frozen with HES.

REPORT DATE: 04/15/93 WORK UNIT # 6038

DETAIL SUMMARY SHEET

TITLE: Collection and Cryopreservation of Spleen Cells for the Production of Monoclonal Antibodies

KEYWORDS: spleen, cryopreservation, lymphocyte

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Fischer, Gerald COL MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Apr 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To use cryopreserved spleen cells from a bank as a source of growth factors and tumor monoclonal antibodies.

TECHNICAL APPROACH

After splenectomy, spleen is dissected and single cell suspensions are made. These cells are cryopreserved in liquid nitrogen for later use.

PRIOR AND CURRENT PROGRESS

In the past year, no new registrants have been accrued. This study is now closed to further registrants. No studies utilizing this cell bank have been done in the reporting year. Cells currently frozen in the cell bank will be stored at the Department of Pediatrics' laboratory of the Uniformed Services University of Health Sciences until no longer viable.

CONCLUSIONS

This study is completed; no further registrants will be accepted.

REPORT DATE: 02/16/93 WORK UNIT # 6062

DETAIL SUMMARY SHEET

TITLE: The Effect of Mestinon on Growth in Non-growth Hormone Deficient Short Children

KEYWORDS: short stature, growth hormone, pyridostigmine

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether Mestinon (pyridostigmine) has a physiological effect on growth hormone secretion and hence on growth.

TECHNICAL APPROACH
Mestinon (60 mg) or placebo will be given each night at bedtime to short, non-growth hormone deficient children. Growth rate and serum somatomedin C will be compared (between 6 months of Mestinon therapy and 6 months of placebo) for placebo versus drug treatment.

PRIOR AND CURRENT PROGRESS
To date, 11 patients have been enrolled on this protocol (none during the past year). No complications of treatment have occurred. However, since growth rates on treatment were not significantly different from those during the placebo period, no further patients will be placed on this protocol.

CONCLUSIONS
Mestinon given at bedtime to non-growth hormone deficient children with short stature did not change their growth rates. These results are being prepared for publication.

REPORT DATE: 08/25/93 WORK UNIT # 6064

DETAIL SUMMARY SHEET

TITLE: The Effect of Somatomedin C on Androgen Receptor and 5-a-reductase Activities in a Hormonally Responsive Tissue, the Penile Foreskin

KEYWORDS: somatomedin C, androgen, 5-alpha-reductase

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $14,246 Previous FYs: $ 18,685 Total: $ 32,931

STUDY OBJECTIVE
To determine whether or not growth hormone (GH) acting through its effector hormone, somatomedin C (IGF-1), has in vitro effects on androgen receptor activity or 5-alpha-reductase activity in the penile foreskin.

TECHNICAL APPROACH
Primary explant fibroblast cultures will be prepared from five normal infant foreskins at the time of routine circumcision. Confluent monolayer cultures will be used to assay 5-alpha-reductase activity by the conversion 3H-testosterone to H-dihydrotestosterone and metabolites, as well as androgen receptor activity assayed by specific binding of 3H-dihydrotestosterone to whole cell preparations.

PRIOR AND CURRENT PROGRESS
Cultures of foreskin fibroblasts have been established and maintained in the laboratory for study. Prior progress has shown that IGF-1 has proliferative effects on these cell cultures. Current studies have shown that testosterone increases the production of IGF-1 and IGF-binding protein by these cultures. Immediate plans are to follow through on this observation with studies using anti-IGF-1 antibody to evaluate the importance of this change in the proliferative effects of testosterone on foreskin fibroblasts.

CONCLUSIONS
Study is continuing to be productive in new understanding of the roles and interactions of androgens and growth factors in the regulation of fibroblast growth.

REPORT DATE: 07/19/93 WORK UNIT # 6219

DETAIL SUMMARY SHEET

TITLE: Chronic Stress, Change in Social Support, and Uncertainty

KEYWORDS: chronic stress, reactions to stress

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To evaluate psychological, physiological, and behavioral responses to ongoing chronic stress; b) To examine the role of change in the stress-social support relationship; and c) To determine the role of ambiguity or uncertainty in stress.

TECHNICAL APPROACH

A multi-modal (endocrine, hematologic, psychiatric, immunologic) evaluation is used for family members of children with malignancies. This study is in conjunction with the Department of Psychiatry, USUHS. Families are screened by a hematology-oncology nurse specialist.

PRIOR AND CURRENT PROGRESS

Subject recruitment was completed at WRAMC for this study in July 1992. The total WRAMC enrollment was 86; however, only 80 will be evaluable for this study. Analysis of results is being conducted at the Uniformed Services University of Health Sciences by Andrew Baum, MD, Depatment of Medical Psychology. Although several manuscripts are planned, none are yet reported by Dr. Baum.

CONCLUSIONS

This study is completed at WRAMC (subject accrual and data analysis). Inquiries regarding study results are being answered by Dr. Baum at (301)295-3270 or his study assistant, Sondra Zakowski, at the same phone number.

REPORT DATE: 11/13/92 WORK UNIT # 6223

DETAIL SUMMARY SHEET

TITLE: Ceftriaxone for Outpatient Management of Suspected Occult Bacteremia: A Multicenter Cooperative Study

KEYWORDS: occult, bacteremia, ceftriaxone

PRINCIPAL INVESTIGATOR: Zawadsky, Peter COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare ceftriaxone and Augmentin in the treatment of febrile infants and children who have no obvious focus of infection and who, therefore, may have occult bacteremia.

TECHNICAL APPROACH

This is a collaborative, tri-service multicenter study with Colonel James Bass, Tripler AMC, serving as study monitor. Outpatients fulfilling study entry criteria and consenting to participate are evaluated for occult bacteremia with blood cultures, exam, and other studies as indicated. They are then randomized to therapy with either Augmentin PO or ceftriaxone IM, and follow-up exam is performed 24 hours later. Further evaluation and therapy varies according to symptoms and blood culture results. Data sheets at entry and for each follow-up are compiled. Patients with positive blood cultures will form the study group for comparing the two antibiotic regimens.

PRIOR AND CURRENT PROGRESS

No additonal patients have been enrolled since the last report. A total of 519 patients were enrolled since the approval date.

CONCLUSIONS

No difference between ceftriaxone and Augmentin has been found. These findings have been submitted for consideration for publication. The study is closed.

REPORT DATE: 03/10/93 WORK UNIT # 6231

DETAIL SUMMARY SHEET

TITLE: Advanced Airway Management Skill Station Using Cats

KEYWORDS: endotracheal, intubation, cats

PRINCIPAL INVESTIGATOR: Restuccia, Robert LTC MC
ASSOCIATES: Bley, John Jr. MAJ VC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To teach orotracheal intubation to pediatricians and pediatric nurses attending the Pediatric Advanced Life Support Course (PALS) at Walter Reed Army Medical Center. Using live cats enables the students to practice on a model which simulates intubation of infants and children.

TECHNICAL APPROACH

Cats are anesthetized with ketamine and acetylpromazine in order to permit orotracheal intubation while maintaining spontaneous respiration. If needed, the cats receive topical lidocaine on their vocal cords to diminish laryngospasm and intramuscular atropine to reduce airway secretions. Each cat is limited to five attempted orotracheal intubations, after which it is returned to the holding cage and monitored until it recovers from anesthesia.

PRIOR AND CURRENT PROGRESS

Three PALS courses were conducted since the last report. Seventy-eight providers have been taught intubation skills in this laboratory. The number of PALS courses has been expanded to four each year at WRAMC, and 12-16 cats are used in each interaction of the laboratory. Last year, a total of 44 cats were used. An endotracheal intubation of a cat with a flexible bronchoscope was videotaped for use in future classes as an additional teaching aid.

CONCLUSIONS

The animal intubation laboratory used as part of the Pediatric Advanced Life Support Course should be continued. Investigators will consider means of doing so; to include the possible submission of another protocol.

REPORT DATE: 01/15/93 WORK UNIT # 6256

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Tumor Necrosis Factor on the Function of the Pituitary Gonadotrophs of the Rat

KEYWORDS: F, pituitary

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 1,796 Previous FYs: $ 1,308 Total: $ 3,104

STUDY OBJECTIVE
To determine if tumor necrosis factor affects the secretion of LH from cultured pituitary cells of the rat.

TECHNICAL APPROACH
Pituitary cell cultures will be established from acutely dispersed cells. Fresh cells must be prepared for each experiment. Cells will be stimulated with GnRH, and the LE released will be measured by Rat LH-RIA. TNF will be added in parallel experiments to determine if it blocks GnRH stimulated LH release.

PRIOR AND CURRENT PROGRESS
The methods for establishing pituitary cell cultures have been used in this lab to establish short-term pituitary cultures. No further study has yet been done to elaborate an effect of TNF on pituitary function.

CONCLUSIONS
This study is worthy of further effort to investigate the effects of TNF and other cytokines on pituitary function. Now that the effects on gonadal function are somewhat defined, this portion of the study should now be able to proceed.

REPORT DATE: 01/15/93 WORK UNIT # 6257

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Tumor Necrosis Factor on the Function of the Gonadal Axis of the Rat

KEYWORDS: TNF, gonad

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $17,442 Previous FYs: $ 19,579 Total: $ 37,021

STUDY OBJECTIVE
To determine if tumor necrosis factor (TNF) has an effect on testosterone (T) production in the testis.

TECHNICAL APPROACH
Leydig cells will be separated and cultured from acutely dispersed testicular cell preparation. Cells will be incubated with hCG and TNF to determine if TNF inhibits T production.

PRIOR AND CURRENT PROGRESS
Macrophage conditioned media (containing several cytokines) has been shown to decrease the production of testosterone, cAMP, and dihydrotestosterone. The mechanism of this effect is the current area of investigation, and there are suggestions that this might be mediated through changes in either cGMP or NO formation. Current efforts are looking at these second messengers.

CONCLUSIONS
This study is progressing well toward publication and should be further along in definition of mechanism within the next 1-2 years.

REPORT DATE: 01/15/93 WORK UNIT # 6258

DETAIL SUMMARY SHEET

TITLE: Polymorphism of Prolactin in Neonatal Cord Blood

KEYWORDS: prolactic, neonatal

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,667 Total: $ 1,667

STUDY OBJECTIVE
To determine if prolactin (PRL) exists in multiple species in human cord blood, and, if so, whether or not these different species have different biological activity.

TECHNICAL APPROACH
Cord blood is to be collected from the placenta after delivery of the infant and after detachment from the mother. Serum will be separated and frozen for analysis over G-100 sephadex column chromatography. PRL will be identified by radioimmunoassay (RIA), and biological activity will be assessed by NB2 rat node lymphoma cell bioassay.

PRIOR AND CURRENT PROGRESS
No samples were ever obtained from Obstetrics Service for this study. Request that this study be closed.

CONCLUSIONS
None.

REPORT DATE: 04/29/93 WORK UNIT # 6266

DETAIL SUMMARY SHEET

TITLE: High Dose Chemotherapy with Autologous Bone Marrow Rescue in Children with Recurrent or Progressive Solid Tumors or Primary CNS Malignancies, Phase II

KEYWORDS: autologous, marrow transplantation, solid malignancy

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define the toxicities of the preparative regimen high dose Cytoxan, etoposide, and carboplatin. To measure response rate in a group of patients with refractory solid tumors and CNS malignancies following this regimen and autologous bone marrow transplantation (ABMT).

TECHNICAL APPROACH
Patients 21 years old or less will be entered in the study. After marrow is harvested and stored, ablative chemotherapy will be given for 5 days, followed by a day without chemotherapy. The next day, stored marrow will be reinfused as a "rescue" for the marrow damaged by the intensive therapy. This protocol accepts registrants who are refractory to other treatments for solid tumors and CNS tumors. Response will be evaluated at 60 days post marrow reinfusion.

PRIOR AND CURRENT PROGRESS
In the past year, 4 registrants were entered on study (total now 11). There have been no unexpected toxicities in any registrants. Response at day 60 post-ABMT was: four in complete remission, four in partial response, one with stable disease, and two with progressive disease. To date, 7 out of the 11 patients remain alive.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/05/93 WORK UNIT # 6267

DETAIL SUMMARY SHEET

TITLE: The Value of Sequential C-Reactive Protein Levels in Sickle Cell Anemia Patients Presenting with Symptoms of Crisis or Infection

KEYWORDS: sickle cell disease, c-reactive protein

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 372 Previous FYs: $ 0 Total: $ 372

STUDY OBJECTIVE
To study the clinical value of sequential c-reactive protein (CRP) levels in the differential diagnosis of bacterial infection vs. sickle crisis, and to compile data on age-related ranges of CRP values found in children with sickle cell anemia.

TECHNICAL APPROACH
CRP levels for baseline will be taken at time of regular checkups in the Outpatient Hematology Clinic and updated every 6 months. At the time of presentation with symptoms of bacterial infection or sickle crisis, CRP values will be taken at set intervals and compared to the registrant's baseline. After the event is diagnosed by standard methods, differences in CRP values will then be analyzed.

PRIOR AND CURRENT PROGRESS
To date, 35 samples have been taken from 11 patients (no new registrants this past year); lagging behind planned accrual. There have been no serious or unexpected adverse reactions. This project has lost momentum due to lack of trainee involvement over the past year. After preliminary evaluation of data, a new trainee will be assigned to this study if justified.

CONCLUSIONS
Study should remain open pending interim evaluation.

REPORT DATE: 10/16/92 WORK UNIT # 6274

DETAIL SUMMARY SHEET

TITLE: Assessment of Meconium Suction Techniques in the Piglet Trachea

KEYWORDS: meconium, suction, efficacy

PRINCIPAL INVESTIGATOR: Wiswell, Thomas LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 165 Total: $ 165

STUDY OBJECTIVE
To compare the efficacy of techniques for removing meconium from an in vitro piglet trachea model; and to evalaute the histopathologic effect on the airway of effective suction techniques; specifically, whether suction pressure, pattern, or presence of meconium impacts histopathologic changes.

TECHNICAL APPROACH
Fourteen suction techniques were tested in each of 14 in vitro piglet trachea. Three efficacious techniques were selected for in vivo comparison. Twenty-four piglets were randomized to one of the three efficacious treatments, either with or without meconium having been instilled into the trachea. After 24 hours the airways were harvested for blinded histopathological assessment.

PRIOR AND CURRENT PROGRESS
Study has been completed. One paper has been published. A second paper is being written at this time.

CONCLUSIONS
The meconium aspirator (made by NEOTECH Corporation) is the best method for removing meconium in vitro. The highest pressures (-150 mm Hg) used continuously (not intermittently) work best (highest retrieval). The meconium aspirator caused minimal damage (histologically) in the in vivo animal model at various points along the trachea when continuous suction at the highest pressure was used.

REPORT DATE: 10/08/92 WORK UNIT # 6275

DETAIL SUMMARY SHEET

TITLE: Modified Immune Serum Globulin in Neonates (1990)

KEYWORDS: IVIG, neonate, RSV

PRINCIPAL INVESTIGATOR: Weisman, Leonard COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 352 Previous FYs: $ 0 Total: $ 352

STUDY OBJECTIVE
To determine the RSV-specific antibody pharmacokinetics of RSVIG in neonates with suspected infection.

TECHNICAL APPROACH
Twenty neonates with suspected infection will be evaluated for RSV infection and treated with a single infusion of 1000/mg/kg of one of two RSVIG preparations. Serum IgG and RSV neutralization titers will be determined prior to infusion, immediately, 1, 4, 8, 11, 14 and 42 days after infusion.

PRIOR AND CURRENT PROGRESS
A total of four patients have been entered into this study. No further patients have been entered since the last report, initially because the product exceeded its shelf life and had to be replaced. Additionally, there have been no eligible patients at WRAMC. Patients will be entered again when the census picks up. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None yet.

REPORT DATE: 06/08/93 WORK UNIT # 6290

DETAIL SUMMARY SHEET

TITLE: Utilization of Foot Length as an Estimation of Gestational Age in the Neonate

KEYWORDS: neonate, gestational age, foot length

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the usefulness of neonatal foot length in the assessment of gestational age in the neonate.

TECHNICAL APPROACH
Foot length is determined on neonates less than 24 hours of age. Each infant will have his or her gestational age determined by maternal dates/ultrasound data, as well as by neonatal Ballard and retinal vasculature exams.

PRIOR AND CURRENT PROGRESS
Forty new patients have been enrolled this past year; 60 altogether. At least 40 more patients need to enrolled over the next year.

CONCLUSIONS
None to date.

REPORT DATE: 06/23/93 WORK UNIT # 6291

DETAIL SUMMARY SHEET

TITLE: Effect of Growth Hormone on the Development of Diabetic Nephropathy in the Rat

KEYWORDS: growth hormone, diabetes, nephropathy

PRINCIPAL INVESTIGATOR: Nickels, David MAJ MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 365 Previous FYs: $ 7,615 Total: $ 7,980

STUDY OBJECTIVE
To prospectively evaluate the possible deleterious effects of growth hormone on the development and progression of diabetic nephropathy in the rat.

TECHNICAL APPROACH
Growth hormone (GH) 0.25mg will be administered daily to diabetic and control rats. Groups of rats will be euthanized at 2 days, 4 days, and 19 weeks to assess the effects of GH at various time intervals. Acute effect of GH at day 2 and day 4 will be determined by analysis of overall kidney hypertrophy and also by analysis of kidney insulin-like growth factor-1 content, as measured by RIA after acid extraction of tissue homogenate. Chronic effects of GH after 19 weeks will be analyzed by measurement of 24 hour urinary albumin excretion by ELISA and by evaluation of kidney histology by light microscopy and electron-microscopy.

PRIOR AND CURRENT PROGRESS
Total number of animals used: 164; serious or unexpected adverse reactions: none. Analysis to date shows the following: 1) Acute effects of GH in the 2 and 4 day studies showed no differences in kidney hypertrophy or intra-renal IGF-1 content between the GH treated diabetic vs control diabetic rats. Both diabetic groups showed an equivalent level of kidney hypertrophy acutely. 2) Chronic effects of GH (19 weeks): a) Rats treated with GH had significantly higher weight gain overall; b) Diabetic rats overall had larger kidney hypertrophy, higher urine albumin, excretion, and significant histopathologic changes correlated with early diabetic nephropathy; and c) There was no significant difference in kidney weight, UAE, or histopathology between diabetic/control rats vs diabetic/GH rats.

CONCLUSIONS
Short-term administration of GH over 2-4 days to diabetic rats does not worsen the early kidney hypertrophy seen with diabetes, nor does it change the intra-renal IGF-1 content. Chronic high-dose GH administration (19 weeks) to diabetic rats does not worsen the subsequent development of diabetic nephropathy.

REPORT DATE: 08/16/93 WORK UNIT # 6295

DETAIL SUMMARY SHEET

TITLE: Comparison of Intravenous and Endotracheal Tolazoline Effects on Hypoxia-Induced Pulmonary Hypertension in Newborn Lambs

KEYWORDS: endotracheal, tolazoline, pulmonary hypertension

PRINCIPAL INVESTIGATOR: Curtis, Jerri LCDR MC
ASSOCIATES: Pettett, Phillip COL MC; Payne, Matthew CPT MS

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 2,552 Previous FYs: $ 16,392 Total: $ 18,944

STUDY OBJECTIVE

To determine whether the endotracheal administration of tolazoline reduces pulmonary vascular resistance in the acutely hypoxic newborn lamb; to compare the effects of endotracheally and intravenously administered tolazoline on systemic vascular resistance during acute hypoxia; and to correlate the clinical effects of endotracheally administered tolazoline with plasma concentrations of tolazoline.

TECHNICAL APPROACH

Using hypoxia as a stimulus for pulmonary arterial vasoconstriction, newborn lambs will be randomized to receive either intravenous or endotracheal administered tolazoline or to serve as a control (receive endotracheal saline). The following cardiovascular parameters will be measured and compared between routes: mean artery pressure, mean pulmonary artery pressure, cardiac output, and pulmonary and systemic vascular resistances. Plasma for tolazoline levels will be obtained at specified time points.

PRIOR AND CURRENT PROGRESS

During the past year, 19 lambs were used and subsequently euthanized; 34 have been used altogether. There were no serious or unexpected adverse reactions. As expected, intravenous tolazoline significantly reduced pulmonary and systemic arterial pressures and pulmonary and systemic vascular resistances. Endotracheal tolazoline significantly reduced pulmonary artery pressure and pulmonary vascular resistance, with less severe systemic vascular effects than IV tolazoline. Statistical differences were identified after 10 animals were treated in each group. Control animals were not significantly affected by the saline injections. Plasma tolazoline levels did not differ significantly between the groups.

CONCLUSIONS

Tolazoline administered endotracheally appears to offer advantages over the intravenous route of delivery. Specifically, a more selective vasodilation of the pulmonary vasculature over the systemic vasculature. This was an acute set of experiments. Therefore, before recommendations for the clinical setting can be made, further investigation is needed. Plasma tolazoline levels did not reflect changes in pressures or resistances in any consistent manner.

REPORT DATE: 06/11/93 WORK UNIT # 6298

DETAIL SUMMARY SHEET

TITLE: In-Vitro Comparison of Three Rapid Latex Agglutination Tests for the Detection of H. Influenzae Type b Antigenuria from Four H. Influenzae Conjugate Vaccines

KEYWORDS: conjugated Hib saccharide, latex agglutination tests

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 755 Previous FYs: $ 400 Total: $ 1,155

STUDY OBJECTIVE
To determine if there is variation in the ability of latex agglutination tests to detect the conjugated Hib saccharide of four conjugated Hib vaccines.

TECHNICAL APPROACH
All vaccines will be diluted in urine to 2 ug/ml. Serial 10 and two dilutions of each vaccine will be tested for the presence of Hib antigen.

PRIOR AND CURRENT PROGRESS
Data collection was presented at the Southern Society of Pediatric Research Annual Meeting, January 1993, New Orleans, LA. The data was also published as an abstract in Clinical Research. No further work is anticipated. Directigen was able to detect as little as 0.5 x .000000001 g/ml of Hboc Hib antigen, while at the other extreme Wellcogen could only detect 1,000 x .000000001 g/ml of PRP-OMP Hib antigen. Four vaccines were tested with three latex agglutination test kits.

CONCLUSIONS
Ther is significant variability in the ability of different latex agglutination test kits to detect conjugated vaccines.

REPORT DATE: 09/23/93 WORK UNIT # 6299

DETAIL SUMMARY SHEET

TITLE: The Neonatal Rat Pup as a Model for Staphylococcus Epidermidis Sepsis in the Newborn: The Effects of a Lipid Emulsion on Survival and Neutrophil Function

KEYWORDS: neutrophil, lipid

PRINCIPAL INVESTIGATOR: Weisman, Leonard COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 7,195 Previous FYs: $ 3,482 Total: $ 10,677

STUDY OBJECTIVE
To establish a suckling rat model for Staphylococcus epidermidis (S epi) sepsis; to determine the pharmacokinetics of two parenterally administered lipid emulsions in the non-infected suckling rat using single and multiple dose regimens; and to determine the effects of parenterally administered lipids in the above animal model and whether these effects are due to changes in neutrophil function.

TECHNICAL APPROACH
One day old suckling rats will be randomly assigned by weight and litter to receive 10^6 - 10^8 cfu of S epi subcutaneously. Serial blood cultures will be taken at 2, 24, and 168 hours to determine rate and clearing of infection. Weights and mortality will be followed for 7 days. Pups will be randomized to receive one of five single or three multiple injections of 10 or 20% intralipid. Blood will be taken at 0, 2, 24, 48, 72, and 168 hours for serum triglyceride levels via direct cardiac puncture after anesthesia. Third stage of this study involves infection of pups receiving intralipid (described above), and measuring growth and survival. Neutrophil assays will be done on rats receiving lipid and S epi.

PRIOR AND CURRENT PROGRESS
The following have been completed: pharmacokinetics of IL in serum of 1 day old suckling rats after various doess of IL; survival and bacteremia studies of 1 day old suckling rats following a) infection with a single clinical strain of s. epidermidis at various doses and b) infection with s. epidermidis and treatment with various does of IL. To date, all animals authorized (153) under this protocol have been utilized. Due to technical difficulties, more animals will be required than anticipated to complete each stage of the protocol. These additional animals will be requested under a protocol addendum, to allow the study of an additional IL preparation and assays on neutrophils from suckling rats treated with and without IL.

CONCLUSIONS
Physiologic doses of IL did not effect survival, growth, or bacteremia in s. epidermidis infected suckling rats, though high doses increased infection and mortality. A suckling rat model has been established for s. epidermidis sepsis that is not dependent on lipid therapy. Serum triglyceride levels of IL therapy is reached.

REPORT DATE: 10/16/92 WORK UNIT # 6300

DETAIL SUMMARY SHEET

TITLE: The Use of Surfactant Therapy During the Early Management of the Meconium Aspiration Synbdrome in a Piglet Model Ventilated with Either High Frequency or Conventional Mechanical Ventilation

KEYWORDS: meconium aspiration, surfactant, ventilation

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 2,520 Previous FYs: $ 23,003 Total: $ 25,523

STUDY OBJECTIVE

To determine if use of surfactant therapy will improve physiologic parameters, result in less severe histologic findings, or reduce surface tension measurements in a piglet model of the meconium aspiration syndrome.

TECHNICAL APPROACH

Meconium will be insufflated into piglet trachea, followed by randomization to either conventional or high frequency ventilation. A standard dose of surfactant will be administered 1 hour later or the piglets are randomized to twice the standard dose. Physiologic parameters will be followed during the 6 hours of ventilation. After euthanasia, histologic evaluation of the lungs will be performed (using a previously published scoring system). Finally, surface tension measurements will be made during the course of the experiemnt.

PRIOR AND CURRENT PROGRESS

A total of 70 neonatal piglets were used. The laboratory portion of the investigation is completed. Histologic evaluation by a blinded pathologist is pending.

CONCLUSIONS

To date, there seems to be no improvement in physiologic parameters using either a standard dose or twice standard dose of surfactant. Furthermore, there is no consistent surface-tension lowering after surfactant use.

REPORT DATE: 10/15/92 WORK UNIT # 6301

DETAIL SUMMARY SHEET

TITLE: High Dose Chemotherapy with Autologus Bone Marrow Support Using Ex-Vivo Marrow Treatment with 4-Hydroxyperoxycyclophosphamide (4-HC) for Relapsed Acute Myelogenous Leukemia

KEYWORDS: ABMT, ex-vivo purge, myelogenous leukemia

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn MAJ MC
ASSOCIATES: Burrell, Linda MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the impact of autologous bone marrow support after ex-vivo treatment with 4-Hydroxyperoxycyclophosphamide (4-HC) purging used with a standard preparative (cytotoxic) myeloid regimen for patients with acute myelogenous leukemia who have relapsed.

TECHNICAL APPROACH

Patients diagnosed with acute myelogenous leukemia who are in first or subsequent remission (adults and children) will have bone marrow harvested. One portion of the marrow will be cryopreserved after purging for cancer cells with the drug 4-HC, and the other portion will be cryopreserved without 4-HC purging for use as a backup should anything go wrong with the purged marrow. At the time of relapse (if this occurs), cytotoxic therapy with Cytoxan and busulfan will be given for 1 week, followed by infusion of the purged stored marrow. Patients will be followed for response.

PRIOR AND CURRENT PROGRESS

To date, seven patients have been enrolled on study; one in second remission and six in first remission. All have had bone marrow harvested and purged with 4-HC, and the marrow has been cryopreserved. All harvests were performed at WRAMC. In all but two, the marrow was purged by the WRAMC Bone Marrow Processing Laboratory. The first two marrows were purged at Childrens' Medical Center, Washington, D.C., pending WRAMC approval as an investigative site for 4-HC. There have been no unexpected complications due to the marrow harvest procedure. Sufficient marrow cells were obtained for the storage of an unpurged backup for all but one patient, who has since undergone a second harvest to obtain marrow for the backup. As of yet, no patients have gone on to receive myeloablative therapy and transplantation.

CONCLUSIONS

This study should remain open.

REPORT DATE: 12/11/92 WORK UNIT # 6304

DETAIL SUMMARY SHEET

TITLE: Urinary Tract Infections and the Uncircumcised State - An Update

KEYWORDS: circumcision, urinary tract infection

PRINCIPAL INVESTIGATOR: Wiswell, Thomas LTC MC
ASSOCIATES: Hachey, Wayne CPT MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the frequency of urinary tract infections has changed since the mid-1980's and the effect of circumcision status on these infections; and to perform a meta-analysis of all investigations that have addressed this question to determine if there is a consensus of findings.

TECHNICAL APPROACH
A retrospective record review will be done of all male children born since 1985 in U.S. Army hospitals who were subsequently hospitalized with a urinary tract infection during the first year of life. A meta-analysis of all published studies (nine total) will be performed.

PRIOR AND CURRENT PROGRESS
The chart review and meta-analysis are finished. A total of 476 charts were reviewed. Study is complete.

CONCLUSIONS
The circumcision rate has gone up significantly betwen 1985 and 1990. Uncircumcised boys are 10 times more likely to develop infections. The meta-analysis revealed that all nine published investigations concerning this issue support the association of urinary tract infections with the uncircumcised state.

REPORT DATE: 06/11/93 WORK UNIT # 6305

DETAIL SUMMARY SHEET

TITLE: Isolated Primary Cutaneous Aspergillosis of the Labia

KEYWORDS: aspergillosis, cutaneous, labia

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC
ASSOCIATES: Shoupe, Al MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 2,093 Previous FYs: $ 0 Total: $ 2,093

STUDY OBJECTIVE
To report a very unusual case of isolated primary cutaneous aspergillosis and the first reported case involving the female genitourinary tract.

TECHNICAL APPROACH
A record and literature review will be conducted. Reagents will be ordered to investigate in vitro susceptibility using SAB plates.

PRIOR AND CURRENT PROGRESS
One chart was reviewed for this case report study. The data was published in Medical and Pediatric Oncology, 1993.

CONCLUSIONS
Careful examinations of all body surfaces are critical in immunocompromised patients.

REPORT DATE: 06/11/93 WORK UNIT # 6306

DETAIL SUMMARY SHEET

TITLE: In Vitro Susceptibility of Mycobacterium Avium-Intracellulare to Trimethoprim/Sulfamethoxazole

KEYWORDS: MAC, TMP/SMX, susceptability

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC
ASSOCIATES: McEvoy, Peter MAJ MC; Skillman, Laurie BSc(MT)

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 1,003 Previous FYs: $ 0 Total: $ 1,003

STUDY OBJECTIVE

To detemine if clinical mycobacterium avium-intracellulare (MAC) isolates, which are inherently resistent to most anti-tuberculous drugs, are susceptible to inhibition by trimethoprim/sulfamethoxazole (TMP/SMX) in vitro.

TECHNICAL APPROACH

The susceptiblity patterns of first time clinical isolates of MAC from patients treated at WRAMC will be reviewed. Patients will be categorized as HIV infected or non-infected based upon chart review.

PRIOR AND CURRENT PROGRESS

Seventy-four percent of 275 clinical isolates were susceptible to TMP/SMX at concentrations of 1.25/23.75. No new work will be done. Data was published in Pediatric Infectious Disease Journal, 1993.

CONCLUSIONS

TMP/SMX should be considered as an adjuvant in the treatment of MAC disease, particularly in pediatric patients.

REPORT DATE: 01/15/93 WORK UNIT # 6308

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Cytokines on Placental Steroidogenesis

KEYWORDS: cytokines, labor

PRINCIPAL INVESTIGATOR: Francis, Gary L. LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 2,546 Previous FYs: $ 3,226 Total: $ 5,772

STUDY OBJECTIVE
To determine if cytokines directly affect the production of placental steroids, which might then effect the timing of labor.

TECHNICAL APPROACH
Fragments of human placenta will be established in short-term organ culture and demonstrated to synthesize both progesterone and estradiol from precursors added to culture media. Preliminary studies have shown that cytokines (contained in macrophage conditioned media) decrease progesterone and increase estradiol synthesis. There is a suggestion that this might be associated with a change in PGE2 but not PGF2 production.

PRIOR AND CURRENT PROGRESS
The system for culture, addition of tritiated precursor steroids, and separation of steroid products has been developed. Preliminary studies suggest that cytokines do have the expected effect and that this might be a result of a change in production of prostaglandins.

CONCLUSIONS
This study is progressing well toward preliminary publication. Efforts to further define the mechanism and potential factors which might block this effect are underway.

REPORT DATE: 06/11/93 WORK UNIT # 6312

DETAIL SUMMARY SHEET

TITLE: An Evaluation of the Ability of Human Umbilical Cord Monocytes to Kill K1 Escherichia Coli Following In Vitro Activation with Cytokines

KEYWORDS: neonatal monocytes, cytokines, activation

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC
ASSOCIATES: Cross, Alan COL MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if activation of fresh human infant cord monocytes with cytokines will enhance the in vitro killing of a strain of K1 encapsulated E. coli associated with neonatal meningitis.

TECHNICAL APPROACH
Neonatal monocytes will be separated from cord blood. Monocytes will be cultured, infected with a known number of E. coli organisms, and then cultivated with cytokines. After a set time interval, the killing of the E. coli will be compared between control and cytokine treated groups.

PRIOR AND CURRENT PROGRESS
Little progress was made. The investigator had difficulty obtaining cord blood. Due to heavy time constraints further pilot studies were not undertaken. The project will not be continued.

CONCLUSIONS
No conclusion

REPORT DATE: 03/09/93 WORK UNIT # 6313

DETAIL SUMMARY SHEET

TITLE: Soluble Interleukin-2 Receptor (sIL2R) Levels in New Onset Insulin Dependent Diabetes Mellitus During Biostator Therapy

KEYWORDS: diabetes mellitus, biostator therapy, SIL2R

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC
ASSOCIATES: Curley, Moira MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 1,260 Previous FYs: $ 6,024 Total: $ 7,284

STUDY OBJECTIVE

To determine: (1) if soluble interleukin-2 receptor (SIL2R) levels (an indicator of the level of immune system activation) are elevated in new onset patients with diabetes mellitus and (2) if these levels are suppressed by therapy with the biostator (artificial pancreas), one of the models of intensive insulin therapy currently in use at the University of South Florida (USF), Tampa.

TECHNICAL APPROACH

Serum samples will be obtained from banked (stored) sera, which is under the auspices of a protocol for biostator therapy use at USF and under the custody of Dr. John Malone. These serum samples will be obtained under his protocol and informed consent. No additional blood samples will be obtained, and none will be obtained at WRAMC. SIL2R levels will be determined by enzyme linked immunoassay using commercially available materials.

PRIOR AND CURRENT PROGRESS

Sera have been analyzed from 7 patients and 22 non-diabetic family members. The levels were higher (but not enough to perform statistical analysis) in those with insulin-dependent diabetes mellitus. Attempts to secure additional samples have been exhaustively tried, but due to problems with the WRAMC post office, attempts to obtain additional samples have been unsuccessful. An addendum has been submitted to rectify this problem.

CONCLUSIONS

This study is very interesting, and provocative data is currently available. The only requirement is to obtain additional samples.

REPORT DATE: 05/13/93 WORK UNIT # 6320

DETAIL SUMMARY SHEET

TITLE: Circumcision Following the Neonatal Period

KEYWORDS: circumcision, neonates, infants

PRINCIPAL INVESTIGATOR: Wiswell, Thomas LTC MC
ASSOCIATES: Welch, Catharine Welch CAPT MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To examine a population of children who were circumcised after their newborn hospitalization to determine why the procedure was not performed at that time and why it was performed later; to identify who does the post-neonatal circumcisions, and how it is performed (device, type anesthesia, etc); and to evaluate whether or not there are complications following the later procedure.

TECHNICAL APPROACH

This is a chart review. Data will be obtained from PASBA and from the medical records obtained from U.S. Army medical centers.

PRIOR AND CURRENT PROGRESS

This study has been completed, with 476 charts reviewed. A manuscript has been accepted for publication. The study has been presented at a national meeting, and an abstract has been published.

CONCLUSIONS

The number of boys circumcised after the neonatal period has been increasing since 1985. The complication rate (1.7%) is higher than that of newborn circumcision and seems to be related to the use of general anesthesia. Urologists perform the majority of the procedures.

REPORT DATE: 05/14/93 WORK UNIT # 6321

DETAIL SUMMARY SHEET

TITLE: The Effects of Sex Steroids and Vitamin E on Lipid Peroxidation in the Diabetic Rat Model

KEYWORDS: diabetes, sex steroids, lipid peroxidation

PRINCIPAL INVESTIGATOR: Curley, Moira CPT MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 5,255 Previous FYs: $ 2,209 Total: $ 7,464

STUDY OBJECTIVE

To evaluate the effects of gonadal steroids on lipid peroxidation in the diabetic rat model. The potential protective effects of the antioxidant Vitamin E will also be evaluated.

TECHNICAL APPROACH

Initially, castrated 5-week-old Sprague Dawley rats were used, with puberty initiated using testosterone pellets. This proved unsuccessful; levels of testosterone in an RIA were undetectable. Presently, castrated and intact animals are being used. To induce diabetes, 60 mg/kg streptozotocin is being given. Animals are evaluated for evidence of increased free radicals (the original method of evaluation was felt to be unsuccessful due to the difficulty of recovery of the product); thus, an HPLC method and urinary 8-isoprostane are being used. Evidence of neuropathy is being evaluated after 3 months of being diabetic with an assay which measures for microalbumin.

PRIOR AND CURRENT PROGRESS

Progress to date has shown that there is: (1) a statistically significant increase in the level of 8-isoprostane in the diabetic rat relative to the control, and this correlated with the degree of hyperglycemia; (2) a statistical increase in the amount of recovery of MDA using the HPLC method relative to the MDA assay; and (3) an increased amount of microalbumin in the pubertal diabetic rat relative to the control, but not at a statistically significant level. The number ofanimals used this year (and to date) is 77. There have not been any serious or unexpected adverse reactions.

CONCLUSIONS

There is an increase in the free radical environment in the diabetic animal compared to the control animal, and the evidence of complications is higher in the diabetic pubertal animal relative to the prepubertal animal. Results of isoprostane levels in the pubertal and prepubertal animals are pending, but the expectation is that they will be higher. Investigators hope to show that with Vitamin E, both the levels of isoprostane and microalbumin will improve.

REPORT DATE: 05/25/93 WORK UNIT # 6324

DETAIL SUMMARY SHEET

TITLE: Electrogastrogram and Gastric Emptying in Infants with Hypertrophic Pyloric Stenosis and Gastroesophageal Reflux

KEYWORDS: gastroesophageal reflux

PRINCIPAL INVESTIGATOR: Pineiro, Victor MAJ, MC
ASSOCIATES: Latimer, John COL MC; Pearl, Richard LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 2,005 Previous FYs: $ 0 Total: $ 2,005

STUDY OBJECTIVE

To assess gastric emptying, gastric acid secretion, and gastric electromyography in patients with hypertrophic pyloric stenosis (HPS) and compare to patients with gastroesophageal reflux (GER). Specifically, to determine if there is a correlation between gastric emptying and cutaneous electrogastrogram (EGG) in patients with HPS or GER. Any differences in the EGG amplitude, area under the curve, and frequency in patients with HPS or GER will be compared to controls.

TECHNICAL APPROACH

Infants with apnea, HPS, or GER will be recruited to participate in the study. All patients will undergo an electrogastrogram (similar to an electrocardiogram) to study the electrical potential variations generated by the stomach. The control subjects will be studied once, while the patients with GER and HPS will be studied three or four times to determine the effect of therapy on the EGG. In addition, patients with HPS and GER will also undergo placement of a nasogastric tube to determine the rate of gastric emptying and gastric acid output.

PRIOR AND CURRENT PROGRESS

Due to delays in funding and purchase of equipment, recruitment of patients was initiated in February 1993. To date, one patient with gastroesophageal reflux has been studied. This patient has been studied twice without any serious or adverse reactions. There was no benefit to this particular patient.

CONCLUSIONS

Good quality cutaneous EGG signals can be obtained from infants, and these recordings can be accurately analyzed by the computer programs developed at USUHS. No specific conclusions to the research objectives can be made until more patients are recruited.

REPORT DATE: 06/07/93 WORK UNIT # 6326

DETAIL SUMMARY SHEET

TITLE: The Status of Adolescent Medicine in the Military Health Service System

KEYWORDS: adolescent medicine, military, health care

PRINCIPAL INVESTIGATOR: Robinson, C. Anita MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain the quality and level of health care given to adolescents in the Tri-Service System.

TECHNICAL APPROACH
One hundred randomly selected CONUS and non-CONUS military posts were sent a questionnaire to obtain information on adolescent health care At each site, the questionnaire was sent to departments most likely to service adoloscents; i.e., Emergency Room, Pediatrics, Family Practice, Acute Care Clinic, and Internal Medicine.

PRIOR AND CURRENT PROGRESS
Altogether, 560 questionnaires were mailed to 108 military facilities. There were 277 quesionnaires returned in the first mailing. A reminder notice was sent, and 129 more questionnaires were received. A total of 406 questionnaires were received; all were appropriate for data analysis. Data analysis is currently being accomplished.

CONCLUSIONS
None; research is ongoing.

REPORT DATE: 06/08/93 WORK UNIT # 6327

DETAIL SUMMARY SHEET

TITLE: Effect of Somatostatin on Glomerular PGE2 Production in the Diabetic Rat

KEYWORDS: somatostatin, prostaglandin E2, diabetes mellitus

PRINCIPAL INVESTIGATOR: Nickels, David MAJ MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 7,352 Previous FYs: $ 5,115 Total: $ 12,467

STUDY OBJECTIVE

To study the effects of somatostatin (SRIH), both in-vitro and in-vivo, on the glomerular production of PG E2 as it relates to diabetic nephropathy in the rat model.

TECHNICAL APPROACH

Whole rat glomeruli will be isolated from diabetic and control animals and incubated with either SRIH or captopril. PG E2 in the supernatant will be assayed by RIA. The acute effects of SRIH infusion vs saline on the in-vivo renal production of PG E2, as measured by urine PG E2 concentrations, as well as on several parameters of renal physiology (GFR, RPF, RVR, FF) using standard PAH/inulin clearance measurements will be determined. STZ diabetic rats and controls will be treated with SRIH or saline via osmotic pump for 8 weeks, after which urine albumin excretion, urine PG E2, and relative kidney hypertrophy will be measured to determine the more chronic effects of SRIH on these parameters.

PRIOR AND CURRENT PROGRESS

Total number of animals used: 78. Unexpected or serious adverse reactions: none. Analysis to date shows the following: 1) Incubation of glomeruli with both SRIH or captopril results in increased glomerular PG E2 production; 2) Glomeruli from non-diabetic rats appear to be more sensitive to lower concentrations of SRIH than non-diabetic glomeruli; 3) SRIH, when infused IV over 40 minutes to STZ diabetic rats, also acutely increases in-vivo renal PG E2 production as measured as urine PG E2 output; and 4) Longer term (8 weeks) treatment of diabetic rats with SRIH continuously has shown that after 4 weeks of treatment, urinary PG E2 was significantly increased, but not after 8 weeks. Also, a statistical trend toward a significant reduction in albuminaria and kidney hypertrophy was seen with SRIH treatment ($p=0.07$ and 0.10).

CONCLUSIONS

Results of experiments conducted to date are summarized above. Data from experiments to determine if SRIH infusion effects GFR, RPF, RVR, and FF, and if any effects of SRIH are blocked by inhibitors of prostaglandin synthesis, are not yet analyzed. Plans are underway to study the chronic effects of SRIH treatment with a larger number of animals.

REPORT DATE: 06/07/93 WORK UNIT # 6330

DETAIL SUMMARY SHEET

TITLE: Infrared Thermometry in the Evaluation of Localized Infection

KEYWORDS: infrared, thermometry, infection

PRINCIPAL INVESTIGATOR: Miller, James LCDR MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain whether clinical infrared thermometers can be used in the diagnosis of localized infectious processes; such as, cellulitis, septic arthritis, and infectious lymphadenitis.

TECHNICAL APPROACH
This is a validation study. The infrared thermometer will be used to measure the surface temperature over the involved site. A surface temperature will also be measured over an analogous area of the contralateral side of the body. As an additional control, whenever possible, a follow-up measurement will be done over the involved site after resolution of the process.

PRIOR AND CURRENT PROGRESS
The surface temperature as measured by the infrared thermometer has consistently been higher in the involved site than in the contralateral site, and the elevation in temperature decreases with resolution of the process. In some cases, the thermometer has allowed localization of the infection and has demonstrated a temperature difference in lesions prior to development of obvious clinical infection. There have been 18 subjects enrolled to date. There have been no adverse reactions, as is expected in a study of this nature.

CONCLUSIONS
Preliminary results suggest that the infrared thermometer is a useful tool in assisting the diagnosis of localized infectious processes.

REPORT DATE: 07/26/93 WORK UNIT # 6331

DETAIL SUMMARY SHEET

TITLE: In Vivo Dating of the Time Interval from the Initial Presence of Meconium to Birth

KEYWORDS: meconium

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC
ASSOCIATES: Wiswell, Thomas LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 4,500 Previous FYs: $ 0 Total: $ 4,500

STUDY OBJECTIVE
To assess the effect of meconium on changes of placental membranes in a fetal rabbit model. The in-vitro portion will involve the effect of various parameters in changing the color of meconium-stained amniotic fluid.

TECHNICAL APPROACH
1) Inject fetal uteri with meconium of various concentrations and examine after several periods of times (hours to days). 2) Instill meconium-stained amniotic fluid with other substances (acid, base, vernix) and follow color changes over time.

PRIOR AND CURRENT PROGRESS
The study is generally complete. The histology needs to be evaluated and scored, and the photographs of the color changes need to be scored. Twenty-five rabbits have been used for this study. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None made yet.

REPORT DATE: 09/08/93 WORK UNIT # 6332

DETAIL SUMMARY SHEET

TITLE: The Effect of Profound Hypoglycemia on the Release of Excitatory Amino Acids in the Central Nervous System of the Developing Pig

KEYWORDS: hypoglycemia, excitatory amino acids, brain damage

PRINCIPAL INVESTIGATOR: Darling, Bryan LT MC USNR
ASSOCIATES: O'Neill, Timothy PhD; Payne, Matthew CPT PhD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $16,171 Previous FYs: $ 0 Total: $ 16,171

STUDY OBJECTIVE

To determine if acute severe hypoglycemia is associated with the release of aspartate (ASP) and glutamate (GLU) from the newborn piglet brain, if ASP and GLU release differs in older pigs, and if ASP and GLU release is related to brain activity.

TECHNICAL APPROACH

Newborn piglets and adolescent pigs will be anesthetized and ventilated. Femoral arterial and venous lines will be placed for fluid and medications, blood pressure measurements, and blood samples. A sagittal sinus catheter will be placed for blood sampling. A 3mm loop microdialysis probe will be placed in the hippocampus area using stereotaxic surgery, and perfused at 2.5 ul/min with artificial CSF. Six piglets and six pigs will be injected with 200 IU/kg of regular pork insulin, followed by a continuous infusion of 20 IU/kg/hr. All measurements and samples will be collected at baseline, 30 min, 1 hr, 1.5 hr, and 2 hr of severe hypoglycemia. CSF amino acids will be determined by HPLC.

PRIOR AND CURRENT PROGRESS

To date, 12 piglets [1-10 days old (2.5-3.5 kg)] and 12 pigs [8-10 weeks old (20-30 kg)] have been used. There have been no serious or unexpected adverse reactions. As expected, the insulin-treated animals had severe hypoglycemia within 1-2 hr of insulin therapy. The insulin-induced hypoglycemia caused a significant drop in the MAP, while the controls had stable blood pressures throughout the observation period. Blood gases remained stable in all groups. Baseline ASP and GLU levels were significantly higher in both treated and control animals, but during the observation period, ASP and GLU levels did not differ. However, treated piglets' CSF ASP and GLU levels did increase significantly above baseline at approximately 3 hr after insulin administration. The largest contribution to this rise was seen in the piglets who developed isoelectric EEG's.

CONCLUSIONS

Hypoglycemic newborn piglets and adolescent pigs differ in their response to severe hypoglycemia. There is an exaggerated release of ASP and GLU from the brain of the piglet when stressed with severe hypoglycemia, while the pig shows no significant change from baseline. The piglet is particularly prone to have this exaggerated release when hypoglycemia is severe enough to cause a loss of brain activity.

REPORT DATE: 08/04/93 WORK UNIT # 6336

DETAIL SUMMARY SHEET

TITLE: The Use of Saline Lavage and Surfactant Therapy for the Management of the Meconium Aspiration Syndrome in Newborn Piglets - A Model for Intrapartum Management

KEYWORDS: meconium aspiration, saline lavage, surfactant therapy

PRINCIPAL INVESTIGATOR: Giuseppetti, Mary CPT MC
ASSOCIATES: Wiswell, Thomas LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $16,601 Previous FYs: $ 0 Total: $ 16,601

STUDY OBJECTIVE

To assess whether saline lavage, surfactant therapy, or combined saline lavage/surfactant therapy offer any advantage in the early management of the meconium aspiration syndrome.

TECHNICAL APPROACH

The piglet groups will be: saline controls, meconium controls, meconium group treated with saline lavage alone, meconium group treated with surfactant alone, and three meconium groups treated with saline lavage and various dosages/types of surfactants. Piglets will be anesthetized, intubated, and meconium placed into their tracheas via the endotracheal tube. After 15 minutes, airways will be suctioned, and the various treatments done. They will be ventilated for a 6 hour study period, monitoring time multiple oxygenation, ventilation, and pulmonary function parameters, then a chest x-ray will be obtained. They will be euthanized, their lungs removed, and specimens prepared for histologic examination.

PRIOR AND CURRENT PROGRESS

The animal work for this protocol has been completed. Piglets (56) were divided into two control groups and five treatment groups. The piglets were studied during January-March 1993. Two piglets died secondary to equipment malfunction, and one died secondary to pneumothorax. The chest x-rays and the histologic specimens are currently being evaluated. The initial statistical analysis is currently being performed on the oxygenation, ventilation, and pulmonary function data.

CONCLUSIONS

The preliminary statistical evaluations show that the saline control group does not vary significantly from baseline. The remaining groups all received meconium. The data obtained does vary significantly from baseline but not from each other. The preliminary conclusion, therefore, is that the tested therapies offer no advantages. Evaluation of the lung specimens for injury is pending and may show a clinical and statistical difference.

REPORT DATE: 08/09/93 WORK UNIT # 6337

DETAIL SUMMARY SHEET

TITLE: Oxandrolone to Increase Growth in Turners Syndrome Patients: Treatment Protocol

KEYWORDS: Turner's Syndrome, oxandrolone, growth

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To allow oxandrolone, a drug which is only available on IND, to be available for treatment of patients with Turner's Syndrome. This treatment is reported to increase the growth rate and eventual height of these patients.

TECHNICAL APPROACH
Patients with Turner's Syndrome are to be offered oxandroline therapy which is anticipated to increase growth rate. Growth and development will be followed on therapy.

PRIOR AND CURRENT PROGRESS
One patient previously treated with oxandroline has been continued on therapy on this protocol. No new patients have been enrolled to date.

CONCLUSIONS
Patients will be enrolled as planned. It is anticipated that 5-10 patients will be enrolled this year.

REPORT DATE: 01/15/93 WORK UNIT # 6121

DETAIL SUMMARY SHEET

TITLE: POG 7799 Rare Tumor Registry

KEYWORDS: rare tumors, tumors, pediatric tumors

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To accumulate natural history data on malignancies which occur so rarely that larger series of cases cannot be accumulated at any single institution.

TECHNICAL APPROACH
To build a registry which contains pathology review of patients with rare tumors and annual reporting of status of patients.

PRIOR AND CURRENT PROGRESS
In the past year, an additional three cases have been reviewed and accepted (none from WRAMC in the past year), bringing the total reviewed and accepted to 285.

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/15/93 WORK UNIT # 6144

DETAIL SUMMARY SHEET

TITLE: POG 8158 NWTS Long Term Follow-up Study

KEYWORDS: Wilms' tumor, treatment complications

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jan 1982

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To gather epidemiological and late effects data on Wilms' tumor patients.

TECHNICAL APPROACH
Data sent to coordinator to evaluate effects of the cancer and its treatment.

PRIOR AND CURRENT PROGRESS
In the reporting year. there have been 316 new registrants entered on study; 3 from WRAMC. This brings the total number of registrants on study to 3,147 (total of 28 from WRAMC). Foci of study continue to be genetic effects of the disease, and its treatment, pregnancy outcome in survivors, cancer incidence in survivors' offspring, incidence of second malignancies in survivors, and survival.

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/15/93 WORK UNIT # 6175

DETAIL SUMMARY SHEET

TITLE: POG 8532 Treatment of Intracranial Ependymomas, A Pediatric Oncology Group Phase III Study

KEYWORDS: ependymomas, chemotherapy, tumors

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jan 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate the occurrence of seeding of IVth ventricular ependymomas in the CNS after surgery and irradiation to study survival and relapse patterns.

TECHNICAL APPROACH

Careful testing to assess extent of disease after surgery (CT, myelogram, psychological testing, etc.). Testing is repeated after radiation and at 4 to 6 month intervals for 2 years.

PRIOR AND CURRENT PROGRESS

This study closed to accrual in November 1990. It remained ongoing only to report study results, which were expected to be presented in the POG study coordinator reports published bi-annually for POG members. However, this has not been the case. It is expected that this data is being submitted directly to medical journals, rather than being updated bi-annully in the POG reports received. This study is completed now as there were no WRAMC registrants entered. A total of 53 POG registrants were entered.

CONCLUSIONS

Study should be considered closed.

REPORT DATE: 05/26/93 WORK UNIT # 6177

DETAIL SUMMARY SHEET

TITLE: POG 8602 Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC14), A POG Phase III Study

KEYWORDS: lymphocytic leukemia, childhood leukemia, methotrexate

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To treat patients with lymphocytic leukemia in order to provide optimal opportunity for possible cure.

TECHNICAL APPROACH
A comparison of regimens to determine if intermediate dose methotrexate (IDM) and Ara-C in consolidation is superior to IDM + L-asparaginase, and if pulses of IDM/Ara-C at 3 week intervals is superior to pulses at 12 week intervals.

PRIOR AND CURRENT PROGRESS
Study was closed to patient accrual in January 1991; total accrual was 1,951. The status of the 19 WRAMC registrants is as follows: 8 remain alive off therapy, 7 died off therapy, and 4 remain on therapy. Toxicity data was not updated by the study coordinators this year; however, there have been no unexpected or severe toxicites in the four WRAMC patients who remain on therapy.

CONCLUSIONS
Study should remain open for WRAMC registrant follow-up.

REPORT DATE: 06/15/93 WORK UNIT # 6181

DETAIL SUMMARY SHEET

TITLE: POG 8625/8626 Combined Therapy and Restaging in the Treatment of Stages I, IIA, IIIAl Hodgkin's Disease in Pediatric Patients, A Phase II Study

KEYWORDS: Hodgkin's disease, radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To treat Hodgkin's disease in patients staged as I, IIA, and IIIA.

TECHNICAL APPROACH
Effectiveness and toxicities of three cycles of MOPP/ABVD are compared with two cycles of MOPP/ABVD plus radiation.

PRIOR AND CURRENT PROGRESS
This study was closed to patient enrollment in September 1992 when the accrual goal was met. Since the last report, 34 registrants have been enrolled (none from WRAMC). Final accrual totalled 247. To date, five registrants have been treated with progressive disease therapy (8626). Of 223 evaluable patients, the combined complete and partial response rate is 97%. Toxicity has been as expected for this therapy in this population. At this time, there is no statistically significant difference in disease-free survival rate between the two arms (91-93%). WRAMC registrants previously reported remain alive off therapy. No further updates were reported by the study coordinators.

CONCLUSIONS
Study should remain open to follow WRAMC registrants until this data is no longer being reported by the study coordinators in the bi-annual reports.

REPORT DATE: 08/23/93 WORK UNIT # 6184

DETAIL SUMMARY SHEET

TITLE: POG 8653 Study of Childhood Soft Tissue Sarcomas Other than Rhabdomyosarcoma and Its Variants, A POG Phase III Study

KEYWORDS: soft tissue sarcoma, synovial cell sarcoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Aug 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To collect data on tissue sarcomas other than rhabdomyosarcoma and Ewing's; and to treat with surgery, chemotherapy, and radiation.

TECHNICAL APPROACH

To use adjuvant chemotherapy with vincristine, Adriamycin, cyclophosphamide, and actinomycin D (VACA) plus DTIC, when available from manufacturer, after surgery with or without postoperative radiation (POG 8653). DTIC will be given by a randomized decision (when available).

PRIOR AND CURRENT PROGRESS

In the past year, there have been nine new registrants groupwide (total now 99 registrants; none from WRAMC). Preliminary response data in 58 evaluable registrants shows 14 complete responses, 10 partial responses, 3 marginal responses, and 24 with no response. Data analysis is still early, and it is difficult to make conclusions about disease-free survival and response at this point. Toxicity has been as expected for this drug combination used with radiation therapy in this population. There have been no deaths due to toxicity.

CONCLUSIONS

Study should be closed at WRAMC as there are no patients enrolled here, and no further registrations will be allowed on this study.

REPORT DATE: 10/20/92 WORK UNIT # 6188

DETAIL SUMMARY SHEET

TITLE: POG 8650 National Wilm's Tumor Study - 4; A POG Phase III Study

KEYWORDS: Wilms' tumor, renal tumor, nephroblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
a) To gather data on morphology and correlate it with treatment and clinical outcome; and b) To refine clinical trials to reduce therapy to simpler and shorter regimens.

TECHNICAL APPROACH
To attempt to give the usual 5-day course on one day (has been done with other tumors) and to examine in randomized trial with current therapies.

PRIOR AND CURRENT PROGRESS
There have been 2,013 registrants entered on this study altogether (812 since last APR); WRAMC has entered 10 (2 since last APR). All registrants have completed therapy at WRAMC or have been transferred. During the reporting year, a registrant who had completed participation died of progressive disease. Study coordinators report that statistics do not show a difference in efficacy between the study arms yet, nor do they show a difference in toxicity. Accrual for low-risk patients is expected to be completed in the Spring of 1993, and accrual for high-risk patients is expected to be completed in the Spring of 1995.

CONCLUSIONS
Study should remain open at WRAMC.

REPORT DATE: 01/15/93 WORK UNIT # 6191

DETAIL SUMMARY SHEET

TITLE: POG 8616 Intensive Chemotherapies for Stage III Diffuse Undifferentiated Lymphoma (DU NHL Burkitt and Non-Burkitt), A Randomized Phase III Study

KEYWORDS: lymphoma, diffuse, undifferentiated

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Group APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To achieve chemotherapeutic cure in a majority of patients with Stage III DU NHL; to compare two regimens for efficacy and toxicity; and to study correlation between treatment/response and lactate dehydrogenase (LDH).

TECHNICAL APPROACH
Registrants must be 21 years old or less, previously untreated, and Stage III. Randomization is at diagnosis, between "Total B" regimen and a high dose cytoxan/methotrexate regimen.

PRIOR AND CURRENT PROGRESS
As reported last year, study was closed to accrual in November 1991; the total accrual was 135 registrants. Four patients were from WRAMC (no accrual in reporting year); as previously reported, two died of tumor or tumor complications, and two are still alive and disease-free. Major conclusions of the study remain as reported last APR: the total B arm has a trend toward superior remission induction rate; there is also a marginally significant trend favoring the B arm in terms of disease-free survival. No new toxicity data was released by study coordinators, and as reported previously, after 1 year of disease-free survival, there have been no relapses with this disease.

CONCLUSIONS
The two WRAMC registrants have survived beyond the 1 year mark noted by study coordinators (after which no relapses have occurred). Study should be closed at WRAMC.

REPORT DATE: 01/21/93 WORK UNIT # 6192

DETAIL SUMMARY SHEET

TITLE: POG 8651 Osteosarcoma Study 2: A Randomized Trial of Pre-Surgical Chemotherapy Vs. Immediate Surgery and Adjuvant Chemotherapy in the Treatment of Non-Metastatic Osteosarcoma, A POG Phase III Study

KEYWORDS: osteosarcoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine whether pre-surgical chemotherapy will improve survival of subjects with non-metastatic osteosarcoma of the extremity or resectable bone compared to up-front surgery; b) To determine the impact of this approach on limb-sparing procedures; c) To evaluate the relationship of pre-surgery response with prognosis; and d) To study the tumor DNA content as a prognostic factor.

TECHNICAL APPROACH

Eligibility includes age less than 30 years, time less than 3 weeks from diagnosis, no prior history of cancer, and no prior therapy. The tumor must be biopsy-proven high-grade, resectable, and non-metastatic. Chemotherapy includes high-dose methotrexate, Adriamycin, cis-platinum, bleomycin, Cytoxan, and actinomycin D. Pre-surgical chemotherapy randomization lasts 7 weeks.

PRIOR AND CURRENT PROGRESS

There have been four registrants entered on study groupwide in the past year; none from WRAMC. In total, there are 93 registrants groupwide; 1 from WRAMC. The WRAMC patient is still alive. Response remains masked. Toxicity has been acceptable and is as expected for these drugs. Disease-free survival for both study arms combined is currently at 85% during the first year and 73% during the second. Early data on the third and fourth year disease-free survival is currently at 73% and 68%, respectively.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/23/93 WORK UNIT # 6193

DETAIL SUMMARY SHEET

TITLE: POG 8615 A Phase III Study of Large Cell Lymphomas in Children and Adolescents, A Comparison of Two Treatment Regimens, ACOP+ Vs. APO

KEYWORDS: lymphoma, large cell

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine the influence of Cytoxan therapy in advanced-stage large cell lymphomas in children and adolescents by comparing in a randomized prospective study the efficacy and toxicity of the above two modified regimens; b) To study these two regimens without adjuvant XRT and with only 12 months of therapy; and c) To study the clinical and biological characteristics of these large cell lymphomas.

TECHNICAL APPROACH

Registrants less than 21 years old with histologically confirmed large cell lymphomas of Murphy Stage III and IV are eligible. Randomization is at the start of therapy. Modified ACOP+ uses a vincristine/Cytoxan/Adriamycin/prednisone induction, followed by 1 year of multiagent maintenance therapy. Modified APO has a similar induction minus Cytoxan and a similar 12 month maintenance. Both arms are given IT MTX. In December 1991, ACOP+ regimen was closed. Since then, all patients have been assigned to the APO regimen using Adriamycin, vincristine, and prednisone with intrathecal medications given three times.

PRIOR AND CURRENT PROGRESS

There have been 13 new registrants groupwide since last APR. Accrual goals were met in December 1992, and the study was closed to registration at that time (total number of POG-wide registrants is 146; 1 patient from WRAMC). Complete/provisional response rates are currently 97% for the APO regimen, and 95% for the ACOP+ regimen. Disease-free survical rates specific to therapy arm are as yet inconclusive regarding superiority of one arm over the other. Incidence of toxicity has been as expected for the use of the drugs on the study. Data on Adriamycin long-term toxicity will continue to be collected. However, there have been no reports of cardiotoxicity other than the one patient whose experience prompted the decrease of the total Adriamycin dose (reported in previous APR's). The WRAMC patient remains well, disease-free, and without cardiotoxicity.

CONCLUSIONS

Study should remain open at WRAMC to follow the registrant; however, no new accruals will be made on this study. It is not expected that this study will re-open, as a successor study is to be opened soon.

REPORT DATE: 02/22/93 WORK UNIT # 6194

DETAIL SUMMARY SHEET

TITLE: POG 8617/8618 Therapy for B-Cell Acute Lymphoblastic Leukemia and Advanced Diffuse Undifferentiated Lymphomas, A Phase II Study

KEYWORDS: B-cell leukemia, lymphoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Feb 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To estimate CR rate and disease-free survival in patients with Stage IV diffuse undifferentiated (DU) NHL and B-ALL; and b) To estimate reinduction rate and disease-free survival (DFS) for patients in relapse with NHL.

TECHNICAL APPROACH

For POG 8617, children with untreated B-ALL, Stage IV DU NHL, or diffuse lymphoma, non-lymphoblastic histology, in first relapse are eligible. For POG 8618, CNS relapse for NHL with non-lymphoblastic NHL, and isolated CNS relapse of 8617 registrants. Regimen involves initial vincristine/Cytoxan/Adriamycin with intrathecal chemotherapy, followed by IV MTX-Ara-C. POG 8618 (closed 1988) was designed to investigate therapy for patients who relapsed in the central nervous system on this protocol, but closed due to lack of accrual.

PRIOR AND CURRENT PROGRESS

Accrual was completed in November 1992, and the study has not been accepting new registrants since that date. The total accrual reported was 153 groupwide; an additional 28 patients have been enrolled since the last APR. There are no patients enrolled from WRAMC. Complete response rates range from 92% for B-ALL to 100% for stage III DU NHL. Survival rates are promising and show significant improvement over the last POG study of this disease. Toxicity has been lessened over the 6 years of this study with modifications in the therapy plan (1988-change in intrathecal therapy, 1991-addition of G-CSF to therapy). Overall, incidence of toxicity has been as expected for the use of the drugs in this study.

CONCLUSIONS

Study should be considered completed at WRAMC, as there are no patients from this center registered. There are no plans to re-open accrual, as the next POG study for this disease will be activated shortly.

REPORT DATE: 04/20/93 WORK UNIT # 6195

DETAIL SUMMARY SHEET

TITLE: POG 8633/8634 The Treatment of Children Less Than Three Years of Age with Malignant Brain Tumors Using Postoperative Chemotherapy and Delayed Irradiation, A POG Phase II Study

KEYWORDS: medulloblastoma, brain irradiation, infant brain tumor

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine if postoperative chemotherapy in children less than 3 years old with brain tumors will allow delay of cranial irradiation; and b) To assess the response and toxicity rates.

TECHNICAL APPROACH

After surgery, infants are given four drugs over 2 months. If a good response occurs, this is continued for 2 years and then radiation is given. If there is not a complete response, radiation is given earlier.

PRIOR AND CURRENT PROGRESS

As previously reported, POG 8633 has closed for accrual, with accrual goals being met. Study coordinators plan to keep the radiation study open until early 1995 to allow current registrants to be treated with radiation therapy. There has been no report from study coordinators during this reporting cycle, and since there have been no amendments to therapy or other notices, it can be assumed that progress is as expected. Through December 1992, 58 of the 206 patients registered for chemotherapy (8633) progressed on to the joint radiation study (8634). The registrants reported in past APR's have all completed therapy. Two are alive and being followed at WRAMC. Note, the only patients POG may treat on this stuy are those who registered jointly on 8633/34. No new registrants (above the 206) will be accrued on this joint study.

CONCLUSIONS

Study should remain open to follow the two remaining WRAMC registrants.

REPORT DATE: 04/20/93 WORK UNIT # 6196

DETAIL SUMMARY SHEET

TITLE: POG 8741/8742 Treatment of Stage D Neuroblastoma in Children Greater than 365 Days at Diagnosis, A POG Phase II/III Study

KEYWORDS: neuroblastoma, ifosfamide, metastatic neuroblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Apr 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

Phase II: To evaluate response rates in poor prognosis neuroblastoma with Phase II chemotherapy prior to conventional therapy.
Phase III: To evaluate the effectiveness of two chemotherapy regimens in a randomized trial: cisplatin/etoposide/cyclophosphamide/Adriamycin vs. high-dose cisplatin/etoposide/cyclophosphamide/Adriamycin. Data will also be collected to review the effect that tumor resectability has on remission rate and duration.

TECHNICAL APPROACH

Phase II: Cycles of Phase II drugs will be given to evaluate their potential use against neuroblastoma. The first drug is ifosfamide. The response will be evaluated, then conventional chemotherapy will be given.
Phase III: Newly diagnosed patients 365 days old and older who were treated on POG 8741 (Phase II) and failed, or newly diagnosed patients (Stage C and D) who have received no Phase II therapy, are treated with combination chemotherapy and, when possible, surgical removal of tumor.

PRIOR AND CURRENT PROGRESS

The Phase III study (8742) has been closed since November 1991, and the Phase II study (8741) was closed earlier that year. The only remaining WRAMC registrant is well and off therapy. Study coordinators report that for stage D patients on 8742, response has been the same for both treatment arms (complete response rate = 54%). The stage C (better prognosis) patients on 8741, all of whom received the same treatment arm, had a complete response rate of 72%. Toxicity has been as expected for the drug combinations used on this study. The new POG neuroblastoma study for patients over 1 year old is currently being activated.

CONCLUSIONS

Study should be closed at WRAMC. The remaining registrant is expected to continue to do well.

REPORT DATE: 06/09/93 WORK UNIT # 6199

DETAIL SUMMARY SHEET

TITLE: POG 8704: T-Cell #3 Protocol, A POG Phase III Study

KEYWORDS: leukemia, T-cell

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine a) the efficacy of a multi-agent regimen against childhood T-cell leukemia and advanced T-cell lymphoma, b) the advantage gained with addition of high-dose asparaginase to the regimen, and c) the biology of these diseases.

TECHNICAL APPROACH

Children aged 12 months to 21 years are eligible. Simultaneous registration occurs on POG 8600 (leukemia classification protocol). No prior therapy is allowed. The lymphoma must be advanced stage. Pathology review required. Treatment was randomized to *yes or no* L-asp during maintenance, which lasts 90 weeks. CNS irradiation occurs for high white counts and CNS disease.

PRIOR AND CURRENT PROGRESS

This study closed to accrual in January 1992. A total of 557 POG registrants have been enrolled; 4 of them from WRAMC. Updates on results are as follows: induction complete response rates are 97% for both T-cell leukemia and T-cell lymphoma; analysis of disease-free survival for T-cell leukemia registrants who presented with high white blood cell counts (over 50,000 WBC) shows a significant advantage for the use of L-asparaginase during maintenance therapy; and the L-asparaginase containing arm had a greater incidence of infections, hematologic side effects, and allergic reactions. Both WRAMC patients reported previously have completed therapy and remain well (one has transferred to another institution).

CONCLUSIONS

One registrant from this study is to be followed. Study should remain open until study coordinators at POG cease reporting response/disease-free survival at bi-annual meetings.

REPORT DATE: 07/19/93 WORK UNIT # 6204

DETAIL SUMMARY SHEET

TITLE: POG 8751: Low Dose Methotrexate in the Treatment of Rhabdomyosarcoma, A POG Phase II Study

KEYWORDS: methotrexate, rhabdomyosarcoma, POG

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine a) the response rate and duration of response in children with rhabdomyosarcoma treated with low-dose methotrexate (LD MTX) given every 6 hours for 6 doses, and b) the type and duration of toxicity of low dose sustained oral methotrexate.

TECHNICAL APPROACH
This is a single armed Phase II study of children with biopsy-proven rhabdomyosarcoma unresponsive to standard therapy. Patients cannot have had previous exposure to MTX. MTX is given orally every 6 hours for six to eight doses per course and designed to sustain MTX levels of 0.5 micromolar for more than 36 hours per pulse.

PRIOR AND CURRENT PROGRESS
There has been 1 registrant since last APR; total is now 33 (none from WRAMC). Response and survival remain masked. No unusual toxicities have occurred; all have been as expected for this drug at this dose and on this schedule.

CONCLUSIONS
This study should remain open.

REPORT DATE: 08/23/93 WORK UNIT # 6205

DETAIL SUMMARY SHEET

TITLE: POG 8759: The Effectiveness of Phase II Agents in Untreated Metastatic Osteosarcoma or Unresectable Primary Osteosarcoma Vs. Previously Treated Recurrent Osteosarcoma, POG Phase II/III Study

KEYWORDS: osteosarcoma, recurrent, primary

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Aug 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To study the response rate to ifosfamide in newly diagnosed metastatic unresectable osteosarcoma or in osteosarcoma presenting as a second malignancy and to study the addition of the agent to a standard treatment regimen for effectivenes and toxicity; and b) To gain biologic information about the tumor.

TECHNICAL APPROACH

Eligible new patients (biopsy proven) will be treated with two courses of ifosfamide upfront, evaluated for response (including biopsy and a surgical excision), and then continued on standard chemotherapy and ifosfamide. Those registrants having recurrence will continue, if responsive, on ifosfamide only.

PRIOR AND CURRENT PROGRESS

This study was closed to patient accrual in October 1990 and has been open for patient follow-up only since that time. A total of 71 POG registrants have been enrolled; the single WRAMC registrant remains healthy and disease-free. Updated3 year survival and disease-free survival rates submitted at the POG spring meeting were 53% and 39% respectively.

CONCLUSIONS

Although there is continued loss of registrants to relapse and morbidity after 3 years, survival curves are levelling off. There is little reason to keep the study open; recommend closure.

REPORT DATE: 09/23/93 WORK UNIT # 6207

DETAIL SUMMARY SHEET

TITLE: POG 8719: Trial of Shortened Therapy without Maintenance for the Treatment of Localized Non-Hodgkin's Lymphoma, A POG Phase III Study

KEYWORDS: non-Hodgkin's lymphoma, localized

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To compare the survival and disease-free survival in patients receiving 9 weeks of induction/consolidation versus patients receiving similar 9 weeks + 24 weeks of maintenance; and b) To continue cancer biopsy studies of POG #8315.

TECHNICAL APPROACH

Children under 21 years with no prior therapy are eligible. Induction/ consolidation therapy is with Cytoxan/Adriamycin/vincristine and prednisone, with intrathecal medications for head and neck primaries only. Maintenance therapy uses oral 6MP/MTX.

PRIOR AND CURRENT PROGRESS

Study was closed to further registrants in December 1991. A total of 201 POG registrants have been enrolled; the two WRAMC patients remain alive. No new findings have been reported.

CONCLUSIONS

Study should be closed at WRAMC. No further accrual will take place; final findings will be reported in the medical literature.

REPORT DATE: 09/23/93 WORK UNIT # 6210

DETAIL SUMMARY SHEET

TITLE: POG 8761: A Phase II Study of Homoharringtonine for the Treatment of Children with Refractory Nonlymphoblastic Leukemia

KEYWORDS: non-lymphoblastic, leukemia, homoharringtonine

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the efficacy of homoharringtonine (HHT) for the therapy of refractory acute non-lymphoblastic leukemia (ANLL) in children, and further assess the toxicity of HHT.

TECHNICAL APPROACH

Registrants must be a) less than 21 years; b) in relapse, with recovery from prior therapy; c) with no current therapy; and d) with no CNS disease. Treatment is 10 day continuous IV courses, given every 21 days. This study was amended to allow post bone marrow transplant patients who have relapsed to receive this drug.

PRIOR AND CURRENT PROGRESS

There were 32 patients accrued groupwide (6 during the reporting year); none at WRAMC. Out of the 32, 22 were evaluable for toxicity. Toxicities reported were as expected for use of myelosuppressive drugs such as this one. There has been one death of a registrant, which was due to sepsis.

CONCLUSIONS

Study should remain open.

REPORT DATE: 12/18/92 WORK UNIT # 6213

DETAIL SUMMARY SHEET

TITLE: POG 8823/24: Recombinant Alpha Interferon in Childhood Chronic Myelogenous Leukemia, Phase II

KEYWORDS: leukemia, chronic myloid, interferon

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $ 2,559 Previous FYs: $ 12,276 Total: $ 14,835

STUDY OBJECTIVE

To determine toxicity, rate and duration of response to therapy with recombinant alpha-interferon (<-IFN) for newly diagnosed "adult" CML and for "juvenile" CML occurring within the first two decades of life; and to obtain prospective clinical, laboratory, and genetic data on cases of ACML and JCML treated with recombinant <-IFN.

TECHNICAL APPROACH

Qualified registrants must be 21 years of age or less, with no previous treatment, except for emergency lowering of tumor burden. All subjects must meet appropriate specific physical and laboratory eligibility criteria for ACML or JMCL. Monitoring of biologic markers will be performed at several reference labs, including WRAMC Department of Pediatrics lab (serum IFN, B12, LAP, fetal Hb, and muramidase). Patient cells will be separated and cryopreserved at WRAMC and marrow morphology reviewed. IFN will be given as IV daily for 14-day induction, followed by a subcutaneous IFN injection three times a week for maintenance therapy for a minimum of 18 months, according to response.

PRIOR AND CURRENT PROGRESS

There have been 39 registrants entered on study groupwide (none from WRAMC). In the reporting year, there have been seven new registrations. Eight patients have completed 2 years of IFN therapy, eight are still on therapy, and the remaining 23 are either on another therapy or have died. Response data remains masked. Toxicity has remained acceptable; mostly increased liver function tests, decreased platelets, anemia, and neutropenia. Flu syndrome (fatigue, headache, fever, myalgia, etc) was seen in all patients with varying severity. Weight loss has also been seen in many registrants, averaging about 8.6%. Accrual is nearing completion, and the study should close to new registrants during the summer of 1993.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/26/93 WORK UNIT # 6217

DETAIL SUMMARY SHEET

TITLE: POG 8725: Randomized Study of Intensive Chemotherapy (MOPP/ABVD Plus/Minus Low Dose Total Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, IV Hodgkin's Disease in Pediataric Patients, Phase III

KEYWORDS: Hodgkin's disease, nodal radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine in a randomized study whether the addition of low dose total nodal irradiation to four courses of MOPP/ABVD combination chemotherapy will improve the duration of complete remission and survival when compared with patients who have had chemotherapy only.

TECHNICAL APPROACH

Patients are 21 years old and younger who have previously untreated, histologically proven Hodgkin's disease (Stage IIB, III2A, IIIB, and IV).

PRIOR AND CURRENT PROGRESS

Study was closed to patient accrual in February 1992, with a total of 183 registrants groupwide (15 during the past year); 5 patients have been enrolled from WRAMC (none this past year). There were 153 registrants who were fully evaluable (all WRAMC registrants were evaluable). At this time, the addition of low dose total nodal irradiation does not appear to offer an advantage. However, these are early results. Definitive analysis will be completed after 2 more years of patient follow-up. All five WRAMC patients are well and have completed therapy. Toxicity data remains as reported last APR, as does response data.

CONCLUSIONS

Study should remain open to provide follow-up data on WRAMC patients.

REPORT DATE: 09/23/93 WORK UNIT # 6221

DETAIL SUMMARY SHEET

TITLE: POG 8821: Intensive Multiagent Therapy Vs. Autologous Bone Marrow Transplant Early in First CR for Children with Acute Myelocytic Leukemia - A Phase III Study

KEYWORDS: autologous bone marrow, transplant, acute myelocytic leukemia

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine DFS with intensive chemotherapy using non-cross resistant drug pairs; b) To determine if short-term intensive therapy with autologous bone marrow transplant (with 4-Hydroperoxycyclophosphamide purge) is effective therapy; and c) To compare the two regimens' results and to correlate outcome with clinical and laboratory features.

TECHNICAL APPROACH

Registrants are 21 years of age and younger with previously untreated acute myelocytic leukemia (AML). Induction for both arms uses intrathecal Ara-C, daunomycin, Ara-C, 6-TG, followed by high dose Ara-C. Patients are then randomized to receive either IT Ara-C, VP-16/5-AZA plus ABMT with 4-HC purge, or to receive IT Ara-C, HDAC/daunomycin, Ara-C/6-TG, and VP-16/5-AZA.

PRIOR AND CURRENT PROGRESS

A total of 615 patients have been accrued groupwide (143 since last APR); 1 from WRAMC in last year (for a total of 6 patients from WRAMC). This represents the overall necessary study accrual, and the study was closed for registration in March 1993. Toxicity has been as expected for these drugs used in this population. Response duration remains masked, including BMT data.

CONCLUSIONS

Study should remain open for continued evaluation of WRAMC registrants (three still alive, and one still on therapy).

REPORT DATE: 11/23/92 WORK UNIT # 6224

DETAIL SUMMARY SHEET

TITLE: POG 8827: Treatment of Children with Hodgkin's Disease in Relapse, A POG Phase II Study

KEYWORDS: Hodgkin's disease, childhood, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan, MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate overall effectiveness of cytosine arabinoside, cisplatin, and VP-16 in children with Hodgkin's disease in relapse.

TECHNICAL APPROACH

Patients are under 21 yrs at diagnosis and have failed MOPP/ABVD or equivalent treatment. Hodgkin's disease must have progressed beyond consideration that radiation alone might be curative. Separate Ara-C, cisplatin, and VP-16 bolus, with IV infusion of Ara-C in between. One cycle takes 12 hrs, with a total of three injections per cycle. This is repeated every 4 wks for a total of eight cycles, with the option to add two cycles for patients who obtain a CR or PR late in therapy. Radiation therapy following CR or PR is offered on this protocol. In August 1991, the consent form was revised (and IRB approved) to include the increased risk of developing acute myelogenous leukemia after receiving the drug VP-16.

PRIOR AND CURRENT PROGRESS

Study was closed in August 1992 with the completion of accrual goals: 28 patients; none from WRAMC. Overall estimated complete remission rate was 34.6%. Toxicity was mostly hematologic (thrombocytopenia and neutropenia), nausea, and vomiting.

CONCLUSIONS

Study is completed and should be closed at WRAMC.

REPORT DATE: 01/21/93 WORK UNIT # 6227

DETAIL SUMMARY SHEET

TITLE: POG 8862: Treatment of First Marrow and/or Extramedullary Relapse of Childhood Acute T-Lymphoblastic Leukemia and T-Non-Hodgkin's Lymphoma with Combination Chemotherapy Including 2'-Deoxycoformycin

KEYWORDS: first relapse, T-lymphoblastic leukemia, T-non-Hodgkin's lymphoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess toxicity and efficacy of low dose 2'-deoxycoformycin (DCF) in prolonging the duration of second remission of T-ALL/T-NHL. To correlate clinical response and toxicities with plasma levels of the metabolized forms of DCF and the in vitro sensitivity of leukemia cells to the drug.

TECHNICAL APPROACH
Patients 21 years old and less in first relapse of T-ALL/T-NHL are treated with an induction regimen of daunorubicin, vincristine, prednisone, and L-asparaginase. Continuation therapy is IV methotrexate and 6-MP, and registrants are randomized to arms receiving this continuation therapy with or without IV push DCF. Triple intrathecal drugs are given throughout the entire regimen.

PRIOR AND CURRENT PROGRESS
There have been 18 registrants entered on study groupwide this reporting year (none from WRAMC). The total number of registrants is 90 (none from WRAMC). The complete response rate is 64%. Currently, however, the overall event-free survival falls to 8% in the first year. Toxicity is acceptable and is as expected for the drug combination used in this study.

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/21/93 WORK UNIT # 6228

DETAIL SUMMARY SHEET

TITLE: POG 8866: Polyethylene Glycol-Conjugated L-Asparaginase Vs. Native L-Asparaginase in Combination with Standard Agents as Second Line Induction Therapy for Children with Acute Lymphocytic Leukemia in Bone Marrow Relapse. Phase II Randomized Trial

KEYWORDS: PEG L-asparaginase, relapsed ALL, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jan 1989

FUNDING: Current FY $ 0 Previous FYs $ 0 Total: $ 0

STUDY OBJECTIVE

To compare in a randomized trial the efficacy, toxicity, and feasibility of administration of PEG L-asparaginase (L-asp) to native L-asp as part of chemotherapy for acute lymphatic leukemia (ALL) in second relapse; and to determine serum half life and duration.

TECHNICAL APPROACH

Patients 21 years old and younger with ALL in second marrow relapse are randomized to receive induction therapy with either PEG L-asp or with native L-asp, plus the drugs vincristine, VP-16, prednisone, ifosfamide, and intrathecal Ara-C, methotrexate, and hydrocortisone. The protocol consent form was revised in August 1991 to include the potential risk of developing acute myelogenous leukemia following treatment with VP-16 and was approved by the WRAMC HUC/IRB the same month.

PRIOR AND CURRENT PROGRESS

There have been a total of 76 patients enrolled on study (3 in the past year). No WRAMC patients were entered. Study closed in May 1992 due to completion of accrual goals. The complete remission rate was 48% overall; the partial response rate was 11%. There is a non-significant (statistically) trend that native L-asparaginase is associated with a higher complete response rate than PEG L-asparaginase. These results should be interpreted with caution, as there was limited power to detect a difference in re-induction rates due to the small sample size. Toxicity data was as expected for these regimens. Incidence of allergic reactions to both forms of L-asparaginase was similar, which is of interest to the investigators. Overall disease-free survival has been poor, with survival at 8% at 1 year. This is as expected for relapsed ALL.

CONCLUSIONS

Study should be closed at WRAMC as there are no patients being followed on study.

REPORT DATE: 01/21/93 WORK UNIT # 6229

DETAIL SUMMARY SHEET

TITLE: POG 8850: Evaluation of Vincristine, Adriamycin, Cyclophosphamide and Dactinomycin with or without the Addition of Ifosfamide and Etoposide in the Rx of Patients with Newly Diagnosed Ewing's Sarcoma of Primitive Neuroectodermal Tumor or Bone. Phase III

KEYWORDS: Ewing's sarcoma, primitive neuroectodermal, childhood tumor

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service
STAT'S: Ongoing
APPROVAL DATE: Jan 1989

FUNDING: Current FY $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare treatment effectiveness of etoposide and ifosfamide added to the standard treatment regimen. To assess toxicity and adverse orthopedic outcome associated with disease and therapies employed. To assess potential significance of tumor characteristics in prognosis.

TECHNICAL APPROACH

Patients aged 30 years old or less will be randomized to receive the standard chemotherapy (vincristine, Adriamycin, and cyclophosphamide) or the standard along with ifosfamide and etoposide. The study was amended to pilot a potential treament for the next study on patients with metastatic disease called regimen C. Patients with metastatic disease will be treated wtih a drug regimen containing the drugs ifosfamide, etoposide, vincristine, Adriamycin, actinomycin-D, and cyclophosphamide.

PRIOR AND CURRENT PROGRESS

There have been 32 registrants entered on study in the last year (no new WRAMC registrants). The total number of registrants is now 198 (1 from WRAMC reported previously). Response remains masked. Toxicity has been acceptable and as expected for these drug regimens. The original goals for accrual have been met (for patients with non-metastatic disease), and accrual has closed on the other two arms. No patients have been enrolled to regimen C, as HUC/IRB approval is pending at this report.

CONCLUSIONS

Study should remain open for patients presenting with metastatic disease.

REPORT DATE: 02/22/93 WORK UNIT # 6233

DETAIL SUMMARY SHEET

TITLE POG 8820 VP-16, AMS, and 5-Azacytidine in Refractory ANLL, Phase II-III Study

KEYWORDS ANLL, refractory disease, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: Ongoing
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous Yrs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare, in a randomized trial, remission rates of VP-16/AMSA vs. VP-16/AMSA and Az in refractory or recurrent acute nonlymphocytic leukemia (ANLL); to determine duration of remission using pulses of induction regimen as continuation therapy; and to study the relative toxicities of the two regimens.

TECHNICAL APPROACH

Pediatric patients who have failed induction or relapsed on frontline therapy are eligible. Induction is 5 days of AMSA, with 3 days of VP-16 (concurrent). Induction is two cycles; a third may be given if patient responds. Maintenance therapy repeated at 4 week intervals. Az regimen includes this drug for 2 days of the cycle.

PRIOR AND CURRENT PROGRESS

There has been one WRAMC registrant; none in the past reporting year. Groupwide, there have been 157 registrants; 19 since the last APR. Response data on evaluable registrants has shown that 45 achieved a complete response, 69 had no response, and 12 died due to disease progression before response was evaluable by protocol guidelines. Accrual is ahead of the projected rate. Differences in toxicity between the two arms have not yet reached significance for predicting the risk of greater toxicity on one arm or the other. Toxicities are as expected for the use of these drugs in relapsed leukemia patients. There were no deaths due to toxicity during the reporting year.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/08/93 WORK UNIT # 6236

DETAIL SUMMARY SHEET

TITLE: POG 8829 A Protocol for a Case Control Study of Hodgkin's Disease in Childhood

KEYWORDS: childhood, Hodgkin's disease, epidemiology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: McFarland, Janetta MAJ AN; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To collect specific data on the epidemiology of childhood Hodgkin's disease (HD). Parameters to be examined are: possible variance between adult and chilhood forms of HD, patterns of previous infectious disease exposure, socioeconomic patterns, familial aggregation, and risk for other diseases. b) To evaluate the parameters listed above according to histologic subtype, stage, and age at diagnosis.

TECHNICAL APPROACH

Newly diagnosed HD patients, ages 15 years and less, seen at POG institutions will complete (the parents will complete) a questionnaire by phone, donate serum for future evaluation, and have clinical study data evaluated. Matched controls will be identified and interviewed over the telephone.

PRIOR AND CURRENT PROGRESS

In the past year, one patient has been enrolled from WRAMC (total now seven). Groupwide there are 505 registrants; 191 since the last report. It is too early to report study results, including incidence of serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/26/93 WORK UNIT # 6242

DETAIL SUMMARY SHEET

TITLE: POG 8828 Late Effects of Treatment of Hodgkin's Disease: A POG Nontherapeutic Study

KEYWORDS: childhood, Hodgkin's disease, long-term effects

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate incidence of late effects following treatment for Hodgkin's disease on current frontline POG studies (8625, 8725) and to attempt to identify pre-treatment and/or on-treatment factors which predict high risk of specific late effects.

TECHNICAL APPROACH
Registrants are patients on POG 8625 or 8725 and are followed through completion of late effects study forms every 3 years.

PRIOR AND CURRENT PROGRESS
On this non-therapeutic study, there have been seven WRAMC registrants interviewed; none this reporting year. Groupwide, there have been 279 registrants; 67 this reporting year. Of the total number of patients registered on POG Hodgkin's disease therapeutic studies, 60% have also enrolled on this survey. Although this is not what the study coordinator had projected, accrual appears to be adequate, so far, towards reaching a total that can provide a strong statistical analysis of the data.

CONCLUSIONS
Study should remain open at WRAMC.

REPORT DATE: 05/26/93 WORK UNIT # 6243

DETAIL SUMMARY SHEET

TITLE: POG 8863 High Dose Cytosine Arabinoside in the Treatment of Advanced Childhood Tumors Resistant to Conventional Therapy, Phase II

KEYWORDS: recurrent/refractory, solid tumors, cytosine arabinoside

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine efficacy and toxicity of various advanced refractory solid tumors to high-dose Ara-C (HDAC).

TECHNICAL APPROACH

Patients are 21 years old and younger at diagnosis with biopsy-proven, measurable, malignant solid tumor, life expectancy greater than 6 weeks, adequate nutritional status, blood counts, renal and hepatic function, and no previous HDAC. HDAC is given over 3 days, with about 3 weeks in between cycles.

PRIOR AND CURRENT PROGRESS

This study was permanently closed to accrual in December 1991 (27 patients had entered groupwide). No WRAMC registrants were enrolled on this study. It was expected that study coordinators would report further response data in the POG meeting agendas, which could then be reported here. However, this data is to be published in the medical literature instead.

CONCLUSIONS

Study should be closed.

REPORT DATE: 05/26/93 WORK UNIT # 6244

DETAIL SUMMARY SHEET

TITLE: POG 8865 Recombinant Alpha Interferon in Relapsed T-Cell Disease: A Phase II Study

KEYWORDS: interferon, T-cell, malignancy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess response rate of T-cell malignancy to alpha-IFN (<-IFN) who have failed standard therapy. To correlate response rate to presence of IFN receptors, oncogene receptors, modulation of oncogene expression, modulation of oncogene expression by IFN, DNA content, and antiproliferative effect of IFN in-vitro on T-cell lymphoblasts.

TECHNICAL APPROACH

Patients 21 years and younger with refractory T-cell disease in second marrow relapse, meeting entry requirements concerning previous therapy, and with no evidence of serious uncontrolled infection are eligible for this study. Induction of triple intrathecal methotrexate, high-dose cytoxan, and Ara-C is given and continued with pulse maintenance therapy. Induction IFN is given for 5 days x 2 weeks, followed by 3 x week maintenance course.

PRIOR AND CURRENT PROGRESS

This study met accrual objectives and was closed May 1992. There have been no WRAMC registrants entered on this study. Final groupwide accrual was 21 patients (2 since the last APR). Response is as follows for 17 evaluable patients: 0% complete response, 53% partial response, 18% mixed response, and 29% no response. Toxicity has been as expected for the use of alpha interferon in this disease.

CONCLUSIONS

This study should be closed because there are no patients on this study from WRAMC, and accrual is closed.

REPORT DATE: 07/19/93 WORK UNIT # 6250

DETAIL SUMMARY SHEET

TITLE: POG 8935 A Study of Biological Behavior of Optic Pathway Tumors

KEYWORDS: optic pathway tumors, children, biology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To assess time to progression in patients with optic pathway tumors (OPT) and with or without neurofibromatosis; b) To estimate response at 2 years post-radiation therapy; c) To estimate incidence of progression in patients with neurofibromatosis; d) To assess long-term effects of being treated for OPT under the age of 21; and e) To assess the value of neurophysiologic techniques in the assessment of disease progression and response.

TECHNICAL APPROACH

Patients 21 years old and less with previously untreated OPT. If disease progresses when registrant is over 5 years old, either radiation therapy for 6 weeks or surgery with or without radiation therapy will be given. If registrant is 5 years old or less, carboplatin will be given on POG protocol 8936 (WU# 6251).

PRIOR AND CURRENT PROGRESS

In the past reporting year, there have been 38 new registrants entered in the study. The total is now 82 registrants (none from WRAMC). It is too early to report response data. Toxicity data show side effects are as expected for the drugs used in this study.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/19/93 WORK UNIT # 6251

DETAIL SUMMARY SHEET

TITLE: POG 8936 Carboplatin in Progressive Optic Pathway Tumors: Phase II

KEYWORDS: carboplatin, optic pathway tumors, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the response rate to carboplatin (CBDCA) in children with optic pathway tumors, and to assess the efficacy of CBDCA in delaying the progression of disease.

TECHNICAL APPROACH

Registrants on POG 8935 who are 5 years old or less, who have evidence of optic pathway tumor progression, are given IV CBDCA over 1 hour every 4 weeks for 18 months.

PRIOR AND CURRENT PROGRESS

There have been 20 registrants entered on study since last report; the total is now 38 registrants (no WRAMC patients have been registered on this study). It is too early to report response data. Toxicity data was evaluable in 20 patients so far; toxicity has been as expected for the drugs used in this population.

CONCLUSIONS

Study should remain open.

REPORT DATE: 10/20/92 WORK UNIT # 6252

DETAIL SUMMARY SHEET

TITLE: POG 8945: An Intergroup Protocol for the Treatment of Hepatoblastoma and Hepatocellular Carcinoma, Phase III

KEYWORDS: hepatoblastoma, hepatocellular carcinoma, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare response rates of hepatocellular carcinoma and hepatoblastoma in patients less than 21 years of age when treated with either Adriamycin and cisplatin or cisplatin/5FU/vincristine. Also, to compare the event-free survival rate and toxicity of the two regimens. Serum alpha-fetoprotein levels will also be studied to determine their value as a relapse predictor. Pure fetal histology tumors are also to be studied.

TECHNICAL APPROACH

Patients less than 21 years old with hepatocellular carcinoma or incompletely resected, unfavorable histology hepatoblastoma are randomized to receive either cisplatin and Adriamycin or cisplatin/5FU/vincristine. Response is evaluated and resection performed as indicated. Serial serum levels of alphafetoprotein and ferritin will be drawn, and their relationship to relapse will be analyzed. Favorable histology hepatoblastoma will be treated with Adriamycin and response evaluated.

PRIOR AND CURRENT PROGRESS

There have been 74 POG registrants accrued; none from WRAMC. Children's Cancer Study Group has not submitted a report in time for the POG study coordinators to include the CCSG data in this report, so the overall accrual in this intergroup study is not known; only the POG accrual is being reported. For 44 registrants evaluable for response, there have been 18 complete responses, 2 partial responses, 1 marginal response, 8 no response, 7 increasing disease, 7 progressive disease, and 1 early death. Toxicity was evaluable for 56 patients. Neutropenia was the most common toxicity, as expected. There were no reports of unexpected or fatal toxicities.

CONCLUSIONS

Study should remain open.

REPORT DATE: 12/18/92 WORK UNIT # 6253

DETAIL SUMMARY SHEET

TITLE: POG 8930 Comprehensive Genetic Analysis of Brain Tumors

KEYWORDS: brain tumors, children, genetics

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the clinical significance of cellular DNA content, the clinical implications of cytogenetic abnormalities at diagnosis, and of amplification or re-arrangement of proto-oncogenes or allelic loss. To attempt to derive tumor cell lines and a bank of frozen tissue for further studies.

TECHNICAL APPROACH

As pediatric brain tumor patients are registered on POG front-line therapeutic studies, fresh tissue will be submitted for flow cytometry, cytogenetic studies, molecular studies, and cryopreservation, along with peripheral blood specimens.

PRIOR AND CURRENT PROGRESS

There have been 36 patients altogether registered on the study; 24 during the past year. The one WRAMC patient was registered this past year. Study coordinators have not provided an analysis of findings yet, as it is still too early.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/22/93 WORK UNIT # 6260

DETAIL SUMMARY SHEET

TITLE: POG 9046 A Molecular Genetic Analysis of Wilms' Tumors and Nephrogenic Rests

KEYWORDS: Wilms' tumor, cytogenetics

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To define patterns of cytogenetic changes in Wilms' tumor and associated nephrogenic rest tissue and to correlate these patterns with clinicopathologic findings. To establish a bank of molecularly and cytogenetically characterized Wilms' tumors with matched constitutional tissue (lymphoid cells from serum samples).

TECHNICAL APPROACH

Patients 16 years old or less with a previously untreated histologically proven Wilms' tumor of any histological subtype will submit fresh tumor tissue and blood samples for genetic analysis and banking.

PRIOR AND CURRENT PROGRESS

Since the last APR, there have been no new WRAMC registrants (total of five). In the POG, there have been 134 registrants entered since the last APR (total of 250). It is too early for study coordinators to provide a correlation between tumor cytogenetics and treatment outcome.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/22/93 WORK UNIT # 6261

DETAIL SUMMARY SHEET

TITLE: POG 9047 Neuroblastoma Biology Protocol

KEYWORDS: cytogenetics, neuroblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To analyze cytogenetics of neuroblastoma cells and determine the clinical significance of genetic variations found, compared to conventional clinical, histologic, and biologic variables in predicting response to treatment or outcome. To develop a neuroblastoma serum and tissue bank for future studies, and to collect natural history and lab data on patients with untreated disease (stages A and DS).

TECHNICAL APPROACH

All newly-diagnosed patients 21 years old or less who are registered on POG neuroblastoma treatment protocols, or stage A or DS (favorable risk), will submit discarded biopsy material and serum for cytogenetic studies and banking.

PRIOR AND CURRENT PROGRESS

WRAMC total is now one; none since the last report. Groupwide total is now 383; 86 since the last APR. It is too early to correlate the biologic features analyzed on this study with the clinical outcome of the patients. Data regarding the incidence of serious or unexpected adverse reactions is not currently available.

CONCLUSIONS

Study should remain open.

REPORT DATE 03 08 93 WORK UNIT # 5263

DETAIL SUMMARY SHEET

TITLE: POG 9049 A Study of High Risk Malignant Germ Cell Tumors in Children A Phase III Treatment Study

KEYWORDS: malignant germ cell tumor, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy of two regimens: high-dose cisplatin or standard dose cisplatin used with the drugs etoposide and bleomycin. Data will also be gathered on the response at 12 weeks; organ toxicity (acute and long term), prognostic significance of tumor and mestastatic tumor charateristics, significance of several tumor markers at different points in the course of treatment, and tumor and constitutional cytogenetics will be analyzed.

TECHNICAL APPROACH
Pediatric germ cell tumor patients ages 21 years or less with histologically verified disease will be randomized to receive chemotherapy following their surgery with either a regimen of high or standard dose cisplatin, plus etoposide and bleomycin.

PRIOR AND CURRENT PROGRESS
There have been no WRAMC registrants in the past year. The one WRAMC registrant previously reported remains well. Study coordinators publish progress reports for this study in April each year, as it involves data from two cooperative oncology groups (POG and Children's Cancer Study Group). Information in the Fall 1992 progress report is limited to new POG accrual and general comments about toxicity: 1) POG has registered an additional 24 registrants since the last APR (118 altogether); 2) standard dose cisplatin has not resulted in any unexpected toxicity; 3) high dose cisplatin has resulted in a higher incidence of moderate high-frequency hearing loss than is seen with standard dose cisplatin, improved by hearing aids, and 4) three patients have had renal toxicity (stabilized/reversed on completion of therapy). Toxicities (including those listed above) are as expected for the drugs used in this study.

CONCLUSIONS
Study should remain open. Full reports on intergroup accrual, etc., will only be available annually in April. Next APR will include data from the April 1993 intergroup report.

REPORT DATE: 04/08/93 WORK UNIT # 6265

DETAIL SUMMARY SHEET

TITLE: POG 9082 Development of Intervention Strategies to Reduce the Time between Symptom Onset and Diagnosis of Childhood Cancer

KEYWORDS: symptom onset, childhood cancer, diagnosis

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe constellation of symptoms that occur prior to definitive diagnosis of childhood cancer and to evaluate factors that may be associated with the length of time between symptom onset and diagnosis. To determine if these symptoms or time period until diagnosis influence prognosis independent of treatment and disease stage. To provide data that may be used to develop intervention strategies.

TECHNICAL APPROACH
All previously untreated pediatric oncology patients registered on POG treatment studies are registered on this protocol. Questionnaire is given to parents within 7 days of registration on treatment protocol.

PRIOR AND CURRENT PROGRESS
In the past year, 3 patients have been enrolled from WRAMC (total now 18). Groupwide there are 1,272 registrants; 556 since the last report. It is too early to report study results including the incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Study should remain open.

REPORT DATE 05 26 93 WORK UNIT # 6269

DETAIL SUMMARY SHEET

TITLE PBC 9060 Intensive QOD Ifosfamide for the Treatment of Children with Recurrent or Progressive CNS Tumors, Phase II

KEYWORDS: ifosfamide, recurrent brain tumor

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Complete
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the activity of ifosfamide delivered QOD (i.e., M,W,F) in the treatment of children with recurrent/progressive CNS tumors, to evaluate toxicity of this regimen, especially neurotoxicity for patients with (1) no prior cisplatin therapy, (2) prior cisplatin with a total dose less than 300 mg/M2, and (3) prior cisplatin with a total dose greater than 300 mg/M2.

TECHNICAL APPROACH

Patients 21 years old and less with primary intracranial tumor are given ifosfamide three times a week every 21 days as long as the patient continues to demonstrate at least stable disease.

PRIOR AND CURRENT PROGRESS

Since the last APR, there have been no WRAMC registrants (total from WRAMC=0). Groupwide, there have been 14 patients registered in the reporting year (total=83). Response and survival remain masked. Toxicity has been as expected for this drug when used at this dose. The study has been closed as of April 1993 due to completion of accrual goals.

CONCLUSIONS

Study should be closed, as there are no registrants to follow, and accrual is completed.

REPORT DATE: 06/09/93 WORK UNIT # 6270

DETAIL SUMMARY SHEET

TITLE: POG 9048 The Treatment of Children with Localized Germ Cell Tumors, Phase II

KEYWORDS: localized, malignant germ cell tumor, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine long-term, event free survival for better risk patients treated with surgery alone; to determine long-term, event free survival for poorer risk patients treated with cisplatin, etoposide, and bleomycin; and to determine prognostic significance of tumor histology, site, size, tumor cytogenetics, and constitutional sex chromosomes.

TECHNICAL APPROACH

Pediatric patients 21 years old and less with good risk malignant germ cell tumors are treated with surgery alone and observed for increase in tumor marker levels. If tumor markers rise, good risk patients are treated, as are the other tumor histologies eligible for this protocol, with four cycles of cisplatin, etoposide, and bleomycin. Tumor tissue cytogenetic studies are also done on all registrants.

PRIOR AND CURRENT PROGRESS

Since last report, there have been 68 registrants entered on this study groupwide; which brings the total number registered to 119 (there have been no WRAMC registrants). Response and disease-free survival are masked in this study. Toxicity has been as expected for these drugs in this population.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/09/93 WORK UNIT # 6271

DETAIL SUMMARY SHEET

TITLE: POG 9061 The Treatment of Isolated Central Nervous System Leukemia

KEYWORDS: infant leukemia, CNS relapse

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the feasibility and toxicity of intensified systemic treatment with delayed craniospinal radiation for children with acute lymphoblastic leukemia (ALL) and isolated central nervous system (CNS) disease. To study the pharmacokinetics and cytotoxic effect within the cerebrospinal fluid (CSF) of intravenous 6 MP given as a single agent in an up-front treatment window.

TECHNICAL APPROACH

Children less than 1 year old and with ALL in first marrow remission with isolated CNS relapse are given intravenous 6-MP for 2 weeks before a second induction, consolidation, and intensification chemotherapy regimen, followed by craniospinal irradiation and a 76 week maintenance period.

PRIOR AND CURRENT PROGRESS

Since last report, there have been 21 new registrants groupwide (total now 62); 1 has been from WRAMC (total now 2). One WRAMC patient has completed therapy on protocol and remains well; the other registrant is still on therapy. Study completed accrual goals and has closed to further registrants. The remaining registrants have already completed induction therapy (all had a complete response), and the study remains open to allow these patients to be treated and followed. Overall, the 6-MP upfront (pre-induction therapy) did not prove to be efficacious in clearing disease from the central nervous system. Out of 62 patients on study, 6 have relapsed. Toxicity on study has been as expected for these drugs used in this population.

CONCLUSIONS

Study should remain open at WRAMC to follow registrants.

REPORT DATE: 07/19/93 WORK UNIT # 6272

DETAIL SUMMARY SHEET

TITLE: POG 9031 The Treatment of Children with High Stage Medulloblastoma: Cisplatin/VP-16 Pre Vs. Post Irradiation, Phase III

KEYWORDS: cisplatin, radiotherapy, medulloblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare survival of children treated with and without pre-irradiation chemotherapy. To determine if c-myc gene amplification in medulloblastoma is associated with an adverse prognosis.

TECHNICAL APPROACH

Children between the ages of 3 and 21 years are randomized to receive either pre-irradiation chemotherapy with cisplatin and VP-16, followed by more cycles of chemotherapy or a second treatment; which is irradiation followed by chemotherapy with cisplatin and VP-16. Specimens are sent to a central office to determine c-myc amplification.

PRIOR AND CURRENT PROGRESS

There have been 48 registrants entered on this study since the last report; total is now 100 registrants on study (1 from WRAMC, reported last APR). Response is masked. Toxicity has been as expected for these drugs used in this population. The WRAMC patient is stable off therapy.

CONCLUSIONS

Study should remain open.

REPORT DATE: 12/18/92 WORK UNIT # 5278

DETAIL SUMMARY SHEET

TITLE: POG 9000 Acute Lymphocytic Leukemia in Childhood #15 Classification Protocol: A Non-therapeutic Study

KEYWORDS: ALL, children, laboratory analysis

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To standardize classification procedures of acute lymphocytic leukemia (ALL) in children with either good risk or poor risk of relapse. To study various features of diagnostic bone marrow and peripheral blood samples and relate these features to treatment outcome.

TECHNICAL APPROACH
Samples of peripheral blood and bone marrow obtained at diagnosis from patients ages 21 years and less are sent to several reference labs at other institutions. Results are obtained after several days to ensure that the patient has been categorized correctly as either good risk or poor risk by the local hospital (WRAMC), and that the patient has been offered the appropriate treatment protocol. Data compiled on laboratory features of registrants on this protocol will be related to their treatment response.

PRIOR AND CURRENT PROGRESS
There have been 990 patients registered on study groupwide; 362 during the past year. Of these 853 have gone on to be treated on the POG frontline acute leukemia protocols. Eleven WRAMC patients have been enrolled; 5 during the past year. All 11 WRAMC registrants have been registered on POG frontline studies. To date, study coordinators have reported on the rates of occurrence of the different lineage leukemias (B-cell, T-cell, non-T, non-B, unclassifiable) and several other parameters of interest. It is too early to correlate findings from the reference laboratory to treatment outcome.

CONCLUSIONS
Study should remain open.

REPORT DATE: 12/18/92 WORK UNIT # 6279

DETAIL SUMMARY SHEET

TITLE: POG 9005 Dose Intensification of Methotrexate and 6-Mercaptopurine for ALL in Childhood, Phase III

KEYWORDS: ALL, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine in a randomized trial the most effective way to give methotrexate and 6-mercaptopurine to maintain remission in children with acute lymphocytic leukemia (ALL) at low risk for relapse. Also, to determine the relevance of methotrexate levels to treatment success.

TECHNICAL APPROACH

Newly diagnosed patients, ages 1-21 years, with ALL in first remission will be randomized to receive one of three regimens using the drugs 6-mercaptopurine and methotrexate. All regimens last about 2.5 years. Results will be compared between treatment regimens, stratifying registrants for various possible prognostic factors. During 1992, therapy on study was revised so that methotrexate alone will no longer be given as CNS antileukemia therapy; all intrathecal therapy will use hydrocortisone, methotrexate, and Ara-C. WRAMC registrants were told of this change.

PRIOR AND CURRENT PROGRESS

There have been 463 registrants enrolled groupwide; 172 during the past year. At WRAMC, there have been seven registrants (four this reporting year); all but two have transferred to other hospitals. Overall, complete response rates have ranged from 87.5%-100% in the four strata, the lowest being for patients with Philadelphia chromosome (+) disease. Toxicity has been tolerable and appears to be more pronounced later in therapy than at induction/early intensification. The most frequently reported toxicities experienced by the 294 evaluable registrants are; neutropenia - 48%, diarrhea - 32%, stomatitis - 15%, increased liver function tests - 10%, bacterial infections - 7%, and infections of no documented source - 7%.

CONCLUSIONS

Study should remain open.

REPORT DATE: 12/18/92 WORK UNIT # 6280

DETAIL SUMMARY SHEET

TITLE: POG 9006: Acute Lymphocytic Leukemia in Children Study #15: Up Front Alternating 6-MP and Methotrexate Vs. Up Front Alternating Chemotherapy

KEYWORDS: ALL, poor risk, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare in a randomized trial the efficacy and toxicity of 12 courses of IV methotrexate/6-mercaptopurine vs. 12 alternating courses of methotrexate/6-mercaptopurine, VM-26/Ara-C, and daunomycin/Ara-C in children with acute lymphocytic leukemia (ALL) who are high risk for relapse.

TECHNICAL APPROACH

Newly-diagnosed non-T, non-B ALL patients, 1-21 years of age, with poor prognostic features will be randomized to receive one of two treatments, both lasting about 2.5 years. Registrant response will be analyzed by stratum (registrants are grouped by disease prognostic factors; such as, disease in the central nervous system, cytogenetic factors, etc.).

PRIOR AND CURRENT PROGRESS

There have been 189 registrants groupwide; 38 during the past year. There have been 4 from WRAMC; 1 during the past year. As the accrual rate has been much higher than projected, the National Cancer Institute approved an amendment to improve the statistical power of the study by increasing the study's duration from 26 months to 39 months. This amendment was approved by the WRAMC IRB. Of the four WRAMC patients, one died this year after relapsing and being placed on another therapy (BMT at Johns Hopkins). The other three remain on therapy at WRAMC and are in remission. Preliminary results show a complete response rate between 80-100%, depending on stratum. The poorest responders on the study are those with CNS. Induction is well tolerated, and the most significant toxicities appear to occur later in therapy. In 125 eligible registrants, 58% had neutropenia, 40% had mucositis, 18% had increased LFT's, and 19% had thrombocytopenia.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/21/93 WORK UNIT # 6281

DETAIL SUMMARY SHEET

TITLE: POG 9140 Treatment for Recurrent or Refractory Neuroblastoma

KEYWORDS: neuroblastoma, recurrent, pediatric

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the response rate and toxicity of three chemotherapy regimens used to treat neuroblastoma that has not responded to initial treatment, and to determine the effectiveness of using retinoic acid to prolong the time to relapse in patients who respond to the chemotherapy regimens on this study. Also, to measure retinoic acid receptors and determine their role in predicting response and toxicity.

TECHNICAL APPROACH

Patients 21 years old and less who have neuroblastoma and have not responded to initial therapy efforts will be randomized among three arms of chemotherapy: 1) cisplatin/sodium thiosulfate/VP-16, 2) CBDCA/VP-16, and 3) ifosfamide/CBDCA. Those who achieve a response will be maintained on retinoic acid. Randomization will be done in a sequential fashion; the first group of patients to present will be treated with Arm 1, and so on. The consent form was revised and approved by the IRB in July 1991 for amendments (addition of the drug G-CSF as supportive therapy and the closure of regimen 1).

PRIOR AND CURRENT PROGRESS

There have been 18 patients entered on study since the last report; 1 from WRAMC. Groupwide the total number on study is 37; 2 from WRAMC. Accrual is expected to be completed in 2 years. Subjective and objective responses have been observed in five patients who received regimen 1 induction therapy. All other response data is masked at this time. Toxicity has been as expected for the use of the drugs in this trial. The surviving WRAMC patient is currently on therapy.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/08/93 WORK UNIT = 6285

DETAIL SUMMARY SHEET

TITLE: POG 9107 The Treatment of Acute Lymphocytic Leukemia in Infants: Phase III

KEYWORDS: infant, leukemia, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine toxicity of 1 year of intensive post-induction chemotherapy with a combination of the drugs Ara-C, DNR, 6-MP, methotrexate, vincristine, VP-16, prednisone, and Cytoxan, to determine the feasibility of this regimen for use in a groupwide Phase III pilot. After this regimen is piloted in 20 patients, the drug GM-CSF will be added to the drug regimen.

TECHNICAL APPROACH

The drugs listed above are given over a 2 year period to children who are less than 1 year old with the diagnosis of acute lymphocytic leukemia. After 20 registrants receive this therapy, the role of GM-CSF in this age group will be addressed by its addition to the study, providing that Phase I data supports that this drug is safe and effective in infants for the lessening of severity and duration of neutropenia associated with chemotherapy. G-CSF proved to be acceptable therapy in this age group and was added to the study (IRB approval September 1992).

PRIOR AND CURRENT PROGRESS

There have been no WRAMC registrants. Groupwide, 11 patients have been registered since the last APR (total now 28). Out of 17 evaluable registrants, 16 have achieved complete remission (CR); however, there have been 7 relapses within the first year. Only 3 of 10 patients in CR have reached the 300th day. Event-free survival so far is not substantially different on historical comparison with the predecessor POG study. Toxicities have been as expected for the drugs used on this study and have not exceeded the incidence or severity that is expected with their use. As mentioned above, G-CSF (not GM-CSF) has been approved as part of the treatment regimen.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/08/93 WORK UNIT # 6287

DETAIL SUMMARY SHEET

TITLE: NPC-1: A Phase II Study of Pre-Irradiation Chemotherapy for Pediaric and Adolescent Patients with Nasopharyngeal Carcinoma

KEYWORDS: nasopharyngeal, carcinoma, pediatric

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate response to methotrexate/cisplatin/5 FU chemotherapy for children with nasopharyngeal carcinoma, to establish local control rates and patterns of failure with radiation therapy for low stage disease or for chemotherapy plus radiation for high stage disease, and to study the genetic features of this tumor.

TECHNICAL APPROACH
Patients 21 years old and less with nasopharyngeal carcinoma will be treated with radiation alone (low stage disease), or radiation plus the chemotherapy (high stage disease). Tumor tissue removed at diagnostic surgery will also be analyzed at St. Jude for cytogenetic features. (Note: This is a St. Jude study that was extended to other medical centers for participation.)

PRIOR AND CURRENT PROGRESS
Since the last report, there have been 4 registrants, for a total of 17 patients on study. There have been no registrants from WRAMC Toxicity has been very acceptable, with no serious or life-threatening side effects. There have been no distant recurrences. There was one local recurrance, but no tumors have failed to respond. Study coordinators are presenting this study to POG disease committee members this spring and hope to activate it through the cooperative group mechanism.

CONCLUSIONS
Until POG opens a study for nasopharyngeal carcinoma, this study should remain open at WRAMC.

REPORT DATE: 06/09/93 WORK UNIT # 6288

DETAIL SUMMARY SHEET

TITLE: POG 9110: SIMAL #6: Rotational Drug Therapy After First Marrow Relapse of Non-T, Non-B ALL: Pediatric Oncology Group Pilot Study for a Phase III Trial

KEYWORDS: second induction, chemotherapy, leukemia

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold, COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine feasibility and toxicity of continuous infusion doxorubicin when given as a single agent for ALL in first relapse; to assess feasibility and toxicity of a rotating weekly parenteral drug regimen for continuing remission; and to estimate the leukemic cell kill of continuous infusion doxorubicin.

TECHNICAL APPROACH

Patients 21 years of age and less at the time of initial diagnosis with ALL, in first marrow relapse while receiving chemotherapy or after cessation of therapy, will be given continuous infusion doxorubicin to induce remission, followed by 105 weeks of continuation therapy with standard anti-leukemia drugs.

PRIOR AND CURRENT PROGRESS

There have been 69 patients registered groupwide in the past year (none from WRAMC), which brings the total accrual to 141. Accrual goals were met, and the study was closed in December 1992. Updated information on response is: complete response rate = 88%, no response rate = 5%, increasing disease = 2%, and death rate due to disease prior to being evaluable for response = 5%. Compared to prior SIMAL studies, this data looks promising. The 1-year disease-free survival rate is 43.8%, plus or minus 11.6%. The two WRAMC patients reported previously have both died of progressive disease (1 post-bone marrow transplant). Toxicity data for these drugs is as expected in this population.

CONCLUSIONS

Study has been closed to further accrual, and should be considered completed at WRAMC as both registrants from this institution are no longer being followed.

REPORT DATE: 07/19/93 WORK UNIT # 6292

DETAIL SUMMARY SHEET

TITLE: POG 9135: Pre-Radiation Chemotherapy for Children with Supratentorial Malignant Gliomas and Poorly Differentiated Embryonal Tumors of Childhood

KEYWORDS: malignant glioma, embryonal tumor, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate the response of children with supratentorial malignant glioma or poorly differentiated embryonal tumor to three cycles of either BCNU plus continuous-infusion cisplatin or cytoxan plus continuous infusion VP-16; to determine the acute and subacute toxicities; and to estimate the incidence of neuraxis tumor dissemination at diagnosis.

TECHNICAL APPROACH

Following surgical removal or biopsy, children between the ages of 3 and 21 years will be randomized to receive either BCNU plus continuous infusion cisplatin or cytoxan plus continuous infusion VP-16. Treatment is given over approximately 3 months and is designed to be given before radiation therapy (not offered on this study). In July 1992, an addendum was approved requiring the addition of an adverse reaction statement for VP-16 (secondary carcinoma).

PRIOR AND CURRENT PROGRESS

There have been 25 registrants entered on this study since the last APR; total is now 30. The one WRAMC patient reported previously is off treatment with progressive disease and is at home on hospice care. Response remains masked, and toxicity has been as expected for these drugs used in this population.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/19/93 WORK UNIT # 6293

DETAIL SUMMARY SHEET

TITLE: POG 9136: Phase I/II Dose Escalating Trial of Hyperfractionated Irradiation in the Treatment of Supratentorial Malignant Tumors of Childhood

KEYWORDS: supratentorial tumor, radiation therapy, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether radiation therapy can be given at a lower dose than previously used in the treatment of this disease by giving therapy twice a day rather than once a day (doses will be increased in steps, starting with the first group of 20 patients, evaluated for 6 months after therapy) in an attempt to reduce toxicity.

TECHNICAL APPROACH

Twenty patients ages 3 to 21 years with supratentorial malignant neoplasms will be given twice daily radiation therapy over 6 weeks. The dose to be used in this first group will be lower than the dose used in conventional schedule (once daily) radiation therapy for this disease, and will not be increased until toxicity for the first group is evaluated for 6 months. Registrants may have been registered for treatment or biological studies on the POG 9135, the pre-radiation chemotherapy protocol.

PRIOR AND CURRENT PROGRESS

There have been 17 patients registered since last APR; total is now 18 registrants groupwide (1 from WRAMC). The WRAMC patient completed treatment on study, had a partial response, but later had disease progression and is at home on hospice care. Study coordinators report it is too early to provide any other data than number of patients accrued.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/19/93 WORK UNIT # 6294

DETAIL SUMMARY SHEET

TITLE: POG: 9170: Etoposide and Ifosfamide Plus G-CSF in Children with Recurrent Sarcomas: Including Soft Tissue Sarcoma, Ewing's Sarcoma, Rhabdomyosarcoma, and Osteosarcoma: A Pediatric Oncology Group Pilot Study

KEYWORDS: recurrent sarcoma, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish toxicity of VP-16, ifosfamide, and G-CSF when used in children with recurrent sarcomas; to establish a dose level of ifosfamide used with VP-16 and G-CSF; and to establish the acute and chronic dose-limiting toxicities of this drug combination in children after three cycles.

TECHNICAL APPROACH

Children less than 21 years of age are given the drug combination VP-16, ifosfamide, and G-CSF for a maximum of three cycles on study. Ifosfamide dose will be increased in a step-wise fashion after the first group of three patients has received ifosfamide at that dose. Five steps are planned. Study was amended in January 1993 to allow a higher dose of G-CSF to be used, which will result in twice daily rather than once daily administration of the drug. Another amendment was made in March 1993 to better define dose-limiting toxicity as non-hematologic side effects.

PRIOR AND CURRENT PROGRESS

There have been 20 patients registered on study since the last APR; total is now 37 registrants (1 from WRAMC). The WRAMC patient is off therapy (had a partial response, then progressive disease). Response data (other than the patients known here) is masked. Currently, dose escalation has reached level 3 for stratum II (prior exposure to high doses of cisplatin) and to level 5 for stratum I (low dose or no prior exposure to cisplatin). Unexpected toxicity has occurred in roughly 10% of the registrants (Fanconi's syndrome), and there is now increased monitoring of renal function for registrants (January amendment). Other than that, toxicity has been as expected for these drugs.

CONCLUSIONS

Study should remain open.

REPORT DATE: 08/22/93 WORK UNIT # 6296

DETAIL SUMMARY SHEET

TITLE: POG 9150 Intergroup Rhabdomyosarcoma Study IV: STAGE I Disease: A POG Phase III Study

KEYWORDS: rhabdomyosarcoma, chemotherapy, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare survival rates after therapy with one of three drug regimens using the drugs vincristine, actinomycin-D, ifosfamide, cyclophosphamide, VP-16; to evaluate Neupogen as an ameliorating agent during chemotherapy; to evaluate the role of either hyperfractionated or conventional schedule radiation therapy; and to correlate tumor cell biology with clinical course.

TECHNICAL APPROACH
Patients meeting the diagnostic criteria for Stage I disease are given about 13 months of chemotherapy with vincristine and are randomized to receive the drug combinations: actinomycin-D+cyclophosphamide, ifosfamide+VP-16, or actinomycin-D+ifosfamide. Some patients may receive radiation therapy, depending on features of their disease. Clinical group 3 disease requiring radiation therapy will be randomized to receive either hyperfractionated or standard schedule radiation. Total dose of ifosfamide is now limited to 72 g/M2. Patients with pre-existing renal abnormality will be assigned to the arm containing cyclophosphamide. G-CSF will be given after each cycle of combination chemotherapy.

PRIOR AND CURRENT PROGRESS
There have been no WRAMC registrants entered on this study. Study coordinators have reported 52 registrants groupwide; however, they did not provide further data. In October this study was modified due to an increased incidence of renal abnormalities in the arms containing ifosfamide. The drug is now limited to 72 g/M2 total dose and will not be given to patients with pre-existing renal problems. To emeliorate the problems associated with neutropenia, G-CSF is now mandatory support rather than recommended hematologic supportive care. Several changes were also made in the recommendations to surgeons treating patients on this study which involve lymph node biopsy; and were submitted to the IRB October 1992 and approved. The organization of the original consent forms has also been changed; there are now four forms used, depending on disease stage and clinical group.

CONCLUSIONS
Study should remain open.

REPORT DATE: 08/22/93 WORK UNIT # 6297

DETAIL SUMMARY SHEET

TITLE: POG 9152: Intergroup Rhabdomyosarcoma Study IV: Stage IV, Clinical Group IV, and All Patients with Metastatic Disease: A POG Phase III Study

KEYWORDS: rhabdomyosarcoma, chemotherapy, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy of vincristine/melphalan and ifosfamide/VP-16 in a randomized fashion before therapy with standard drugs for this disease (vincristine/Cytoxan/actinomycin-D plus XRT); to evaluate the efficacy of Neupogen in ameliorating neutropenia with this therapy; and to correlate clinical features with tumor cell biology and genetics.

TECHNICAL APPROACH
Patients with Stage IV or with metastatic disease will be randomized to receive combination chemotherapy with melphalan or with ifosfamide/VP-16 before therapy with vincristine/Cytoxan/actinomycin-D plus XRT. Neupogen will be used during periods of neutropenia. Several amendments are currently being submitted to the IRB that were made in October 1992. They also applied to other POG studies (9150, 9151, 9152) and were submitted at the time to the IRB; however, they were inadvertently not submitted for this study.

PRIOR AND CURRENT PROGRESS
A total of 39 registrants have been reported by the study coordinators; there are no WRAMC registrants. No further data is provided in the study coordinator's report to POG.

CONCLUSIONS
Study should remain open.

REPORT DATE: 11/23/92 WORK UNIT # 6302

DETAIL SUMMARY SHEET

TITLE: POG: 9151 Intergroup Rhabdomyosarcoma Study IV: Treatment for Stage 2 and 3 Diseases: A Phase III Trial

KEYWORDS: rhabdomyosarcoma, children, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare progression-free survival of children with rhabdomyosarcoma treated with chemotherapy, radiation, and surgery per protocol; to collect data on the toxicity of these treatments; to correlate disease features (cell biology, tumor size and location, and cytogenetic features) with treatment outcome and survival. Study will also collect material for a tumor tissue bank to use in future tumor biology studies.

TECHNICAL APPROACH

Subjects ages 21 years and less with rhabdomyosarcoma or undifferentiated soft tissue sarcoma will be randomized to receive one of three chemotherapy regimens: vincristine/actinomycin-D/cyclophosphamide, vincristine/actinomycin-D/etoposide, or vincristine/etoposide/ifosfamide. Registrants will also be randomized to receive radiation on a once daily or twice daily schedule. Supportive care with G-CSF will be given. Tumor cytogenetics will be evaluated at a central POG laboratory for future correlations with response data. Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS

Groupwide, this study has accrued 55 patients as of April 1992. At WRAMC, no patients have been entered on this study. At this time, there is no further data available. There was an amendement to the consent forms for this protocol to incorporate changes in requirements for G-CSF administration, total ifosfamide dose, therapy assignment for patients with kidney damage, and time at which surgery is recommended, for certain circumstances, to assess disease response and/or to allow further tumor removal. This amendment was approved by the IRB in October 1992. Groupwide, toxicity has been as expected. The POG will issue a new report in April of 1993 which will give more information regarding serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 11/23/92 WORK UNIT # 6303

DETAIL SUMMARY SHEET

TITLE: POG 9160: Idarubicin Cytosine Arabinoside, for Multiply Recurrent or Refractory ALL: A POG Phase II Study

KEYWORDS: idarubicin, recurrent leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate the re-induction rate with Ara-C and idarubicin for children with acute lymphoblastic leukemia (ALL) in first marrow relapse who failed re-induction on other POG studies. For patients who achieve a complete remission, a uniform maintenance therapy will be used with alternating cycles of VP-16, ifosfamide, idarubicin, and Ara-C. Duration of central nervous system remission will also be estimated.

TECHNICAL APPROACH

Children with ALL in relapse will receive induction therapy with the drugs Ara-C and idarubicin. If there is a response, maintenance therapy with Ara-C, idarubicin, ifosfamide, and VP-16 will be given in alternating cycles. Response data and toxicity data will be collected for use in future studies.

PRIOR AND CURRENT PROGRESS

There have been 25 patients enrolled on study; 1 from WRAMC. Study coordinators report that the induction treatment effectively induces therapeutic bone marrow hypoplasia, which along with consequent fever, neutropenia, and occasional sepsis have been the most frequent toxicities of therapy. There have been two deaths on study due to sepsis following induction therapy. The WRAMC patient did not achieve a complete response and has died of progressive disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/15/93 WORK UNIT = 6307

DETAIL SUMMARY SHEET

TITLE: POG 9130: Treatment of Newly Diagnosed Astrocytomas A Pediatric Oncology Group Phase III Study

KEYWORDS: astrocytoma, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 2,371 Total: $ 2,371

STUDY OBJECTIVE
To determine the role of radiation therapy in the treatment of newly diagnosed patients with astrocytoma; to determine the role of surgical resection; to compare the neuropsychological sequelae of surgery and of radiation therapy; to determine the incidence of malignant transformation of low grade astrocytomas (partially or not resected disease) following radiation therapy; and to study long-term neuroendocrine effects.

TECHNICAL APPROACH
Patients 0-21 years of age with newly diagnosed astrocytoma with radical resection will be followed for neuropsychological effects of surgery and neuroendocrine changes. Patients between the ages of 5 and 21 years with incomplete resection who are neurologically stable will be randomized to receive XRT or no further treatment (but still followed). Patients between the ages of 5 and 21 years who are neurologically unstable or whose physicians refuse randomization will be studied as a separate stratum.

PRIOR AND CURRENT PROGRESS
There have been 34 registrants entered on this study during its first year (none from WRAMC). Although the overall accrual is greater than was expected, accrual to the randomized arm of the study has not been adequate. Study coordinators are currently discussing changing the study's design or closing it. It is too early to report toxicity or response data.

CONCLUSIONS
Until the POG advises WRAMC otherwise, study should remain open.

REPORT DATE: 01/15/93 WORK UNIT # 6309

DETAIL SUMMARY SHEET

TITLE: POG 9132: Hyperfractionated Irradiation for Posterior Fossa Ependymoma: A Phase II/III Study

KEYWORDS: brain tumor, childhood, radiotherapy (XRT)

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study the feasibility and toxicity of twice daily radiation therapy; to study disease control and interval and pattern of failure; and to study the relationship between degree of surgical resection and progression-free survival. Toxicity data to be included in study are neuroendocrine and intellect changes.

TECHNICAL APPROACH

Patients between the ages of 36 months and 21 years with posterior fossa ependymoma will be treated with XRT (1.2 Gy in 58 fractions over 6 weeks; total dose is 69.6 Gy) following biopsy and/or surgical resection. Patients will be followed for disease progression, neuroendocrine changes, and intellectual changes.

PRIOR AND CURRENT PROGRESS

Study opened to registrants on August 26, 1992. To date, study coordinators have reported 17 registrants (none from WRAMC). It is too early to report toxicity data or response data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/15/93 WORK UNIT # 6310

DETAIL SUMMARY SHEET

TITLE: POG 9259: Carboplatin in the Treatment of Newly Diagnosed Metastatic Osteosarcocma or Unresectble Osteosarcoma: A Phase III Study

KEYWORDS: osteosarcoma, chemotherapy, carboplatin

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate response rate to two cycles of carboplatin given before multi-agent chemotherapy; to estimate survival following this therapy; to study the myelosuppressive effects of carbcplatin when renal function and body area (rather than body surface area alone) are used in dose calculations; to relate treatment response to the presence of the multi-drug resistance gene in tumor tissue.

TECHNICAL APPROACH

Patients 30 years old and less with metastatic or unresectable disease at diagnosis will be treated with two cycles of carboplatin chemotherapy, 3 weeks apart, followed by surgical evaluation and resection (if possible). Forty weeks of multiagent chemotherapy will follow the surgery (this multiagent regimen is a proven regimen in the treatment of osteosarcoma), using the drugs methotrexate, ifosfamide, Adriamycin, and cisplatin.

PRIOR AND CURRENT PROGRESS

In the past year, there have been no registrants groupwide. This is acceptable to the protocol's accrual expectations.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/15/93 WORK UNIT # 6311

DETAIL SUMMARY SHEET

TITLE: POG 9182: HIV/Malignancy Biology Study: A Pediatric Oncology Group Aids/Malignancy Network Study

KEYWORDS: AIDS, children, malignancy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish a national registry of HIV-related malignancies in children; to conduct therapeutic trials on these malignancies; and to determine incidence and viral burden of HIV and several other viruses (EBV, CMV, HHV6, HCV) in tumors and body fluids to correlate with other disease and/or treatment information. To study the difference between tumor tissue in HIV positive and HIV negative children.

TECHNICAL APPROACH

Patients 21 years of age or less will be enrolled from three groups: HIV(+) but cancer (-), HIV (-) but cancer (+), and HIV (+) and cancer (+). They will be asked to donate specimens (tumor tissue and body fluids) for the national registry. Cases of HIV-related malignancy will be matched with cases of the same malignancy in a child who does not have HIV. These control cases will be sought from POG registrants in therapeutic trials. So far, studies on viral burden, tumor cytogenetics, and viral incidence are planned for specimens gathered from all three groups. If other factors related to tumor development become uncovered, specimens may be requested from this registry. Chart data will also be collected.

PRIOR AND CURRENT PROGRESS

There have been 12 cases of HIV-related malignancy entered on this study; Burkitt's lymphoma (5), B-cell acute lymphocytic leukemia (3), leiomyosarcoma (2), and reactive hyperplasia (2). Matched controls are being sought.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/08/93 WORK UNIT # 6314

DETAIL SUMMARY SHEET

TITLE: POG 9284/85: Barriers to Enrollment on POG Frontline Therapeutic Clinical Trials and Development of Intervention Strategies: A POG Non-therapeutic Study

KEYWORDS: accrual, oncology treatment

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To prospectively identify factors leading to non-accrual of eligible patients on POG frontline therapeutic studies; and to develop intervention strategies designed to decrease barriers to patient enrollment on POG studies, thus increasing future accrual rates in the POG.

TECHNICAL APPROACH

Patients diagnosed with cancer at POG institutions and their physicians are surveyed within 7 days of their decision whether to participate on POG treatment studies. Survey results from those who decide not to participate (not register on frontline POG study) will be analyzed and compared to the results of those who do register.

PRIOR AND CURRENT PROGRESS

There have been two WRAMC registrants in the past year. Groupwide, 10 patients have been registered since the study opened in February 1992. It is too early to report study results.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/08/93 WORK UNIT # 6315

DETAIL SUMMARY SHEET

TITLE: POG 9280: Neuroblastoma Epidemiology Protocol: A Non-Therapeutic Study

KEYWORDS: neuroblastoma, childhood, epidemiology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the relationship between environmental exposures and the occurrence of neuroblastoma. Environmental factors that will be studied include maternal drug exposures, parental employment in electronic field, and parental radiation exposure. Also to be analyzed are maternal age at birth, length of gestation of patient, and birth weight of patient.

TECHNICAL APPROACH

Mothers of newly diagnosed, histologically confirmed neuroblastoma patients less than 19 years old will be interviewed once over the telephone by trained interviewers. Clinical data will also be provided by the patient's physician. Data will be analyzed to assess risk factors.

PRIOR AND CURRENT PROGRESS

There have been no WRAMC registrants. Groupwide, 10 patients have been registered since the study opened in March 1992. It is too early to report any results.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/08/93 WORK UNIT # 6316

DETAIL SUMMARY SHEET

TITLE: POG 9225: Study for Advanced Stage Hodgkin's Disease: A Phase II Study

KEYWORDS: Hodgkin's disease, advanced stage, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the activity of a new combined modality therapy (irradiation plus the drugs Ara-C/cisplatin/VP-16 and oncovin/procarbazine/prednisone/Adriamycin) and toxicities of this therapy; and to evaluate tumor tissue cytogenetics.

TECHNICAL APPROACH

Patients 21 years of age or less with newly diagnosed advanced stage Hodgkin's disease will be treated with alternating cycles of the drugs listed above, with irradiation. Therapy is given over 6-7 months. Initial biopsy material will be submitted to a central lab for cytogenetic analysis. Modifications to this study have been submitted to the Department of Clinical Investigation and will be reviewed by committee this month.

PRIOR AND CURRENT PROGRESS

There have been no WRAMC registrants. Groupwide, 11 patients have been registered since the study opened in March 1992. Toxicity data from five evaluable patients showed a longer duration and severity of neutropenia in the period following irradiation, resulting in one death Response data has not yet been reported by study coordinators. This is expected in the Spring POG report (circulated in April).

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/08/93 WORK UNIT # 6317

DETAIL SUMMARY SHEET

TITLE: Salvage Therapy for Recurrent Medulloblastoma, Ependymoma, Cerebral Pnet, and Cerebral Low Grade Astrocytoma

KEYWORDS: recurrent brain tumor, childhood, chemotherapy

PRINCIPAL INVESTIGATOR: Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the chemotherapy regimen described below is effective in children with recurrent/refractory brain tumors who have not had prior chemotherapy; and to measure disease-free survival, response rate, and toxicity of this therapy.

TECHNICAL APPROACH
Patients 21 years of age and less with central nervous system malignancies, who have not had prior chemotherapy, will be treated with cisplatin/VP-16 and vincristine/cytoxan, both in combination with G-CSF. These drugs are given in alternating cycles every 3 weeks for a maximum of 9 months. Response to therapy will be measured throughout the study and at regular follow-up. Several hospitals, in addition to Walter Reed, will be using this therapy and will be submitting data to the PI.

PRIOR AND CURRENT PROGRESS
During the first year of this study, no registrants were accrued because no eligible patients consented to enroll. This protocol was activated at three other hospitals: New England Medical Center, Boston, MA (x2); Temple University Hospital, Philadelphia, PA; and Wayne State University Hospital, Detroit, MI.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/08/93 WORK UNIT # 6318

DETAIL SUMMARY SHEET

TITLE: POG 9264: Chemotherapy Regimen for Initial Induction Failures in Childhood ALL: A Phase II Study

KEYWORDS: relapse, childhood, ALL

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate response rate, 1 year disease-free survival rate, and toxicity of using the drugs 6-MP and methotrexate for induction; and to use cDNA probes on tissue samples from patients to look for multi-drug resistant genes and to obtain an oncogene profile.

TECHNICAL APPROACH

Patients, ages 21 years and less, who have failed induction therapy for acute lymphocytic leukemia (ALL) will be given a 3-week induction course of intrathecal chemotherapy and the drugs 6-MP and methotrexate. Consolidation therapy will also be given.

PRIOR AND CURRENT PROGRESS

There have been four patients registered on this study since it opened in April 1992. This is as expected for this disease as treated in the Pediatric Oncology Group. There have been no WRAMC registrants to date. It is too early to report on toxicity or response.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/08/93 WORK UNIT # 6319

DETAIL SUMMARY SHEET

TITLE: POG 9243: Treatment for Children with Intermediate-Risk Neuroblastoma: A Phase III Study

KEYWORDS: neuroblastoma, chemotherapy, surgery

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate response, disease-free survival, and toxicity of therapy (chemotherapy and surgery). For patients receiving intensive chemotherapy, to study the effectiveness of G-CSF in emeliorating neutropenia.

TECHNICAL APPROACH

Infants with stage B, C, or D neuroblastoma or patients ages 1-21 years with stages B, DS, or recurrent stage A neuroblastoma will be treated with chemotherapy and surgery, according to risk factors identified by clinical staging and by tumor cytogenetics. Patients who receive the more intensive chemotherapy will also receive G-CSF therapy in an attempt to ameliorate neutropenia that may result from chemotherapy.

PRIOR AND CURRENT PROGRESS

Study coordinators report that there have been 35 patients registered on this study; however, it is too early to report on toxicity or response. No WRAMC patients have been registered on this study.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/26/93 WORK UNIT # 6322

DETAIL SUMMARY SHEET

TITLE: POG 9222: Mitoxantrone, Etoposide and Cyclosporine Therapy in Pediatric Patients with Relapsed or Refractory Acute Myeloid Leukemia. A P' · II Study

KEYWORDS: ·psed, leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David A COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the genetics of leukemia blast cells in registrants; to look for expression of two genetic mechanisms for drug resistance; and to measure efficacy and toxicity of the drugs mitoxantrone, etoposide, and cyclosporine in children with relapsed or refractory myeloid leukemia.

TECHNICAL APPROACH
Before therapy begins, blood samples will be drawn for genetic studies. Therapy with the drugs listed above will be given for up to 4 months. If relapse occurs after response to these drugs, additional genetic studies will be run on the registrant.

PRIOR AND CURRENT PROGRESS
There have been 11 registrants groupwide on this study since it opened (none from WRAMC). Toxicities for the most part have been as expected for these drugs used in this population. However, because most of the registrants have been treated wi' '. drugs in the past that can lea' to cardiac problems, the incidence of cardiac toxicities has been higher than would normally be expected (2 of 11 had this toxicity). No changes in therapy have been made by the study coordinators, which indicates that toxicity incidence is acceptable.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/26/93 WORK UNIT # 6323

DETAIL SUMMARY SHEET

TITLE: POG 9233/34: A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy <3 Years of Age with a CNS Malignancy Treated With or Without Radiation Therapy

KEYWORDS: brain tumor, child, pre-school, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David A COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study efficacy and toxicity of dose intensified chemotherapy in children less than 3 years old with selected types of brain tumors by means of a randomized comparison; to relate response to DNA index of tumor; and to attempt to observe for disease progression over 1 year, with the option of giving irradiation if tumor relapses during this year.

TECHNICAL APPROACH

Children less than 3 years of age with selected types of brain tumors will be randomized to receive either intensive or standard chemotherapy (POG 9233). If response is adequate, there will be 1 year of close observation, during which time radiation therapy on POG 9234 will be available if the tumor relapses. Patients who have less than adequate response on 9233 will receive irradiation on POG 9234 as soon as possible. The DNA index of diagnostic tumor tissue will be related to the treatment outcome.

PRIOR AND CURRENT PROGRESS

During this first year of accrual, 37 patients were registered groupwide (none from WRAMC). Three of these registrants have progressed/not responded adequately and are receiving radiation therapy on 9234. Response is masked, and study coordinators report it is too early to report on toxicity data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/03/93 WORK UNIT # 6328

DETAIL SUMMARY SHEET

TITLE: POG 9239: Treatment of Children with Newly Diagnosed Brainstem Glioma Using Cisplatin as a Radiosensitizer with Either Conventional or Hyperfractionated Radiotherapy: A Pediatric Oncology Group Phase III Study

KEYWORDS: children, brain tumor, radiation therapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of and to gather data on the toxicity of cisplatin given with cranial irradiation.

TECHNICAL APPROACH
Patients aged 3-21 years will be randomized to receive 6 weeks of cranial radiation with cisplatin given during weeks 1, 3, and 5; with radiation therapy delivered on either a once daily or a twice daily (hyperfractionated) schedule.

PRIOR AND CURRENT PROGRESS
There have been 31 registrants entered on study groupwide since this study opened. WRAMC has registered one patient who recently completed therapy on protocol. This patient tolerated therapy well, with no incidence of serious or unexpected adverse reactions. Response has not yet been measured. Study coordinators have not reported on the data as it is too early.

CONCLUSIONS
Study should remain open at WRAMC.

REPORT DATE: 06/03/93 WORK UNIT # 6329

DETAIL SUMMARY SHEET

TITLE: POG 9296: T-Cell Leukemia Pilot Study #4 (with IV MTX/IV6-MP) A Pediatric Oncology Group Limited Institution Pilot Study (Phase III)

KEYWORDS: T-cell, leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of and to gather further toxicity data on this therapy which substitutes intermediate dose methotrexate and high dose IV 6-mercaptopurine (6-MP) for two drugs on the standard multi-drug regimen for this disease. To sutdy this newer regimen for the feasibility of including it in a two-arm randomized comparison study.

TECHNICAL APPROACH

Patients 1 through 21 years old with T-cell disease (leukemia/lymphoma) will be treated with this 2-year multi-drug regimen. Patients will be followed after completing therapy for late adverse reactions or relapse.

PRIOR AND CURRENT PROGRESS

There have been 30 patients registered on this study since it opened; 1 patient is from WRAMC (doing well on therapy). Response, as expected, has been a 100% remission induction rate. This is similar to the experience on POG 8704, which used the same induction regimen. Toxicity has been as expected, and it is too early to report any further data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/03/93 WORK UNIT # 6333

DETAIL SUMMARY SHEET

TITLE: POG 9237: Idarubicin in Recurrent and Progressive Childhood Brain Tumor Patients: A Pediatric Oncology Group Phase II Study

KEYWORDS: recurrent brain tumor, children, idarubicin

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy and toxicity of idarubicin given with granulocyte-colony stimulating factor (G-CSF).

TECHNICAL APPROACH
Eligible patients 21 years of age and less will be given idarubicin as a 4-hour IV infusion every 3 weeks, followed by G-CSF support until neutropenia resolves. Patients may receive up to six doses of idarubicin on this study. Response will be determined by a review of films at a central office.

PRIOR AND CURRENT PROGRESS
Since the study opened, there have been 29 patients registered groupwide; 2 of these were from WRAMC (1 patient died of progressive disease off study; the other is off study for progressive disease and is at home on hospice care). Study coordinators do not have any responses or disease-free survival data to report at this point. Toxicity, as expected, has been primarily hematologic and has been acceptable for the use of this drug.

CONCLUSIONS
Study should remain open.

REPORT DATE: 07/19/93 WORK UNIT # 6334

DETAIL SUMMARY SHEET

TITLE: POG 9265: Evaluation of 13 Cis-Retinoic Acid in Children with Juvenile Chronic Myelogenous Leukemia: A Phase II Study

KEYWORDS: JCML, cis-retinoic acid, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy and toxicity of cis-retinoic acid in patients with juvenile chronic myelogenous leukemia (JCML), and to determine the relationship between response to treatment and in vitro cell growth patterns.

TECHNICAL APPROACH
Patients, ages 21 years and less with newly diagnosed JCML who are not immediately eligible for bone marrow transplantation, will receive therapy with oral cis-retinoic acid for a minimum of 2 months or until the patient becomes eligible for bone marrow transplantation.

PRIOR AND CURRENT PROGRESS
This study opened in May 1992 and has accrued four patients (none from WRAMC) as is expected for this rare type of leukemia. No further information has been provided by the study coordinators.

CONCLUSIONS
Study should remain open.

REPORT DATE: 07/19/93 WORK UNIT # 6335

DETAIL SUMMARY SHEET

TITLE: POG 9281: Search for Mutations in the p53 Gene From Patients with Osteosarcoma: A Non-Therapeutic Study

KEYWORDS: genetic mutation, osteosarcoma, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of the p53 gene mutation in the genome of patients who have or have had childhood osteosarcoma; and to follow the course of those who have the p53 gene mutation to determine the relationship between this and the occurence of second malignancy.

TECHNICAL APPROACH
Patients diagnosed or treated for osteosarcoma before the age of 31 will be tested for the presence of the p53 genetic mutation. Registrants will be followed for recurrence/second malignancy in order to establish the relationship between this genetic anomaly and cancer. The results of genetic tests will remain masked to the investigator until it is determined the results can provide a benefit to the registrant.

PRIOR AND CURRENT PROGRESS
Study completed accrual goals and was closed in February 1993, with a total of 200 registrants (2 from WRAMC); 70 total POG registrants, 130 non-POG registrants). In the 100 samples completed so far, 2 have shown p53, which is similar to previously reported data on p53/osteosarcoma. One mutation occurred in a ptier who developed a second malignancy.

CONCLUSIONS
Study objective has been met, and this study should be considered completed at WRAMC.

REPORT DATE: 09/23/93 WORK UNIT # 6338

DETAIL SUMMARY SHEET

TITLE: POG 9219: The Treatment of localized Non "odgkin's Lymphoma in Children: A POG Phase IV Study

KEYWORDS: children, lymphoma, localized

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To maintain a high cure rate with minimum toxicity in children with localized non-Hodgkin's lymphoma (NHL) in favorable sites, and to analyze prognostic factors which may predict subgroups of patients with a poorer prognosis within patients with localized NHL.

TECHNICAL APPROACH
Chemotherapy will be given for 3-9 months (depending on stage and location of disease). Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS
This study was opened in September 1992. There have been no registrations from WRAMC; total registration is 38. Preliminary data on 10 evaluable patients shows 9 have achieved a complete response, and none of the 10 have relapsed. No toxicity data was provided by the study coordinators.

CONCLUSIONS
Study should remain open.

REPORT DATE: 09/23/93 WORK UNIT # 6339

DETAIL SUMMARY SHEET

TITLE: POG 9227: Treatment of Recurrent or Refracttory Hodgkin's Disease with Cyclosporine-A, Actinomycin-D, and Vincristine: A POG Phase II Study

KEYWORDS: soft tissue sarcomas, P-glycoprotein, cyclosporine-A

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the toxicity and efficacy of cyclosprine-A (CSA), actinomycin-D (ACT), and vincristine (VCR) in the treatment of recurrent or refractory Hodgkin's disease, Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, or other soft tissue sarcomas; to assess the prevalence of P-glycoprotein (P-gp) in tumor specimens from patients with these diseases, and to correlate this with clinical response to CSA; and to study the pharmacokinetics of high-dose CSA.

TECHNICAL APPROACH
Patients 21 years old or less, with relapsed disease as listed above, will be treated with chemotherapy between 9 weeks and 1 year depending upon response.

PRIOR AND CURRENT PROGRESS
The study opened to accrual in August 1992 and was revised in January 1993 to include patients with recurrent or refractory Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, and other soft tissue sarcomas, as well as Hodgkin's disease. One patient has been registered on this study; none from WRAMC. No further information is available at this time, including incidences of serious or unexpected adverse reactions.

CONCLUSIONS
Study should remain open.

REPORT DATE: 11/05/92 WORK UNIT # 3600

DETAIL SUMMARY SHEET

TITLE: Determination of Noncompliance in Prescription Pickup

KEYWORDS: non-compliance, prescription

PRINCIPAL INVESTIGATOR: Nelson, Bruce COL MS

SERVICE: Pharmacy Service STATUS: Ongoing
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the most common reasons why patients fail to pick up new and refill prescriptions from the Pharmacy. Secondarily, to identify demographically, any significant differences between patients who pick up their prescriptions versus patients who fail to claim their prescriptions.

TECHNICAL APPROACH
Collect an unselected convenience sample of 100 patients with unclaimed, new prescriptions and 100 patients with unclaimed, refill prescriptions. After identifying patients, they will be contacted by phone, asked to participate in the study, and given a short telephone questionnaire. The second part of the study will attempt to identify significant demographic differences between patients who fail to pick up their medication and those who pick up their prescriptions. A random sample of 186 patients in each group (total 372 patients) will be reviewed for differences. Data will be analyzed using logistic regression.

PRIOR AND CURRENT PROGRESS
No questionnaires have been mailed out yet. While some progress has been made on part one of the study, part two of the study has been suspended due to the transfer of the original principal investigator. The investigators request that the study remain in the "ongoing" status while they decide when and who will proceed with it.

CONCLUSIONS
No conclusions have been made.

REPORT DATE: 03/15/93 WORK UNIT # 3603

DETAIL SUMMARY SHEET

TITLE: Ability of Enteral and Parenteral Nutrition to Deliver the Caloric and Protein Goals of Hospitalized Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Nelson, Bruce COL MS

SERVICE: Pharmacy Service STATUS: Terminated
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This protocol has been administratively terminated.

TECHNICAL APPROACH
This protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
This protocol has been administratively terminated.

REPORT DATE: 12/12/92 WORK UNIT # 9609

DETAIL SUMMARY SHEET

TITLE: Radial Nerve F Wave Study

KEYWORDS: F wave response, radial nerve, extensor indicus proprius

PRINCIPAL INVESTIGATOR: Robinson, Michael CPT MC
ASSOCIATES: Fujimoto, Ronald MAJ MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 1,265 Previous FYs: $ 0 Total: $ 1,265

STUDY OBJECTIVE
To obtain a normal latency value for the radial nerve F wave.

TECHNICAL APPROACH
A mean latency value (in milliseconds) will be determined for the F response of the extensor indicus proprius (EIP) muscle, innervated by the radial nerve. Values will be standardized by height. A technique of surface stimulation with cathode placement lateral to the biceps tendon at the flexion crease of the antecubital fossa and surface recording over the EIP muscle will be employed. A Disa 1500 electrodiagnostic machine will be used to provide the stimulation and recording of the F response.

PRIOR AND CURRENT PROGRESS
This protocol has been completed. Eleven studies have been completed since the last report, for a total of 39. No serious or unexpected adverse reactions have occurred. Statistical analyses have been completed. A correlation between height and F wave latency for the radial nerve has been established. Normative values for three height groups were established.

CONCLUSIONS
Subjects under 63 inches (n=17) had mean F wave latencies of 22.3 msec +/- 1.1 msec; 63 to 69 inches (n=18) had mean F wave latencies of 24.0 msec +/- 1.2 msec; and subjects greater than 69 to 74 inches (n=17) had mean F wave latencies of 25.2 msec +/- 0.9 msec.

REPORT DATE: 11/18/92 WORK UNIT # 9612

DETAIL SUMMARY SHEET

TITLE: Epidemiology of Injuries Requiring Physical Therapy During Operation Desert Shield

KEYWORDS: Desert Shield, injuries, physical therapy

PRINCIPAL INVESTIGATOR: Sweeney, Jane COL SP

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 491 Previous FYs: $ 2,058 Total: $ 2,549

STUDY OBJECTIVE
To describe characteristics of injuries requiring physical therapy in mobilized personnel during Operation Desert Shield/Storm in Southwest Asia; to relate injury data to soldier demographics; and to survey workload, work hours, military duties, and professional activities during deployment.

TECHNICAL APPROACH
The method included entry of each new case into the Operation Desert Shield/Storm Physical Therapy Registry at three Persian Gulf combat sites (Bahrain, Riyadh, and Dharan) and at three Germany evacuation sites (Landstuhl, Nurenburg, and Frankfurt). The study design and data management/analysis occurred in Washington, D.C., at the Army Medical Specialist Corps Research Service.

PRIOR AND CURRENT PROGRESS
The Physical Therapy Registry totaled 1,433 cases; 607 (42%) from the combat zone; 826 (58%) from the evacuation zone. Therapy in the combat zone consisted of managing injuries incurred primarily from training (69%) and off-duty (26%) activities; 85% of the referrals were returned to duty. Patients treated by physical therapists in the evacuation zone sustained injuries mainly during combat (75%) or training maneuvers (22%). Twenty-one percent of physical therapy patients in the evacuation zone could have returned to duty (instead of evacuated) if treated in the combat zone by a physical therapist. The treatment duration in the combat zone was 10.7 inpatient days and 1.8 outpatient days. If evacuated to Germany, physical therapy patients were treated an average of 4.3 inpatient days before transfer to USA hospitals. Sites of injury were spine (38%), knee (27%), ankle/foot (12%), upper extremity (11%), hip/thigh (6%), and head (6%).

CONCLUSIONS
The typical physical therapy patient was a 29-year-old Caucasian male with a spine or knee injury incurred 13 weeks after arrival in Southwest Asia. Physical therapists played an important role in expedient assessment and treatment of acutely injured patients in a field environment. The Operation Desert Shield/Storm Physical Therapy Registry is an effective prototype for future deployments.

REPORT DATE: 02/24/93 WORK UNIT # 9614

DETAIL SUMMARY SHEET

TITLE: A Descriptive Analysis of Patient Referrals to Army Physical Medicine Services During Armed Conflict

KEYWORDS: war, rehabilitation, military

PRINCIPAL INVESTIGATOR: Dillingham, Timothy CPT MC
ASSOCIATES: Dillingham, Timothy CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 1,853 Previous FYs: $ 0 Total: $ 1,853

STUDY OBJECTIVE
To describe the patient characteristics of casualties referred to Army physical medicine services during armed conflict. This includes the quantification of functional deficits in these casualties.

TECHNICAL APPROACH
Survey data will be collected at the time of initial contact when a casualty is referred to Physical Medicine. This data will include patient demographics and details regarding the injuries. It will also include functional limitations. There are no modifications to the original protocol.

PRIOR AND CURRENT PROGRESS
All data from the Persian Gulf War Physical Medicine and Rehabilitative Service referrals have been collected and analyzed. The final manuscript has been finished, submitted, and accepted for publication. A subgroup of the Persian Gulf amputees is being written up as another paper describing those particular rehabilitation problems. There were 222 casualties upon whom complete data were collected; musculoskeletal injuries occurred in 56%, nerve injuries in 44%, penetrating wounds in 32%, and fractures in 28%. Electrodiagnostic evaluations were required in 41% of referrals. Limb contractures were noted in 10% of casualties.

CONCLUSIONS
Nerve injuries frequently complicated other injuries.

REPORT DATE: 03/04/93 WORK UNIT # 9615

DETAIL SUMMARY SHEET

TITLE: An Analysis of the Extensor Digitorium Brevis Deep Tendon Reflex in Normals and ir Patients with L5 Radicular Compression Syndromes

KEYWORDS: L5, radiculopathy, reflex

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC
ASSOCIATES: Chang, Audrey PhD

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the extensor digitorium brevis (EDB) deep tendon reflex in patients with L5 radiculopathy and in normals.

TECHNICAL APPROACH
In order to study the EDB reflex and to define its sensitivity along with its latency characteristics, two populations of subjects (normals and patients) between ages 20-60 will be studied. Normals are those without radicular disease. Patients are those with H&P findings compatible with L5 radiculopathy imaging evidence of root compression. The requirement of no back pain within 6 months prior to testing has been eliminated in normals. The EDB reflex will be tested both physically and electrodiagnostically. The EDB response on the patients will be recorded in a blind fashion.

PRIOR AND CURRENT PROGRESS
The data collection and statistical analysis phases have been completed. A total of 83 subjects were enrolled and tested in the study; 13 this past year. Of these, 75 were included in the statistical analysis (those not included did not meet inclusion criteria). No adverse reactions occurred during testing. There was no benefit to the subjects enrolled in the study. At the present time, a manuscript is being prepared. Completion is expected in the next 2-3 months.

CONCLUSIONS
Clinical EDB reflex response (i.e., absent reflex) has a high specificity for L5 radiculopathy. The sensitivity was found to be comparable with that of other current and accepted clinical tests. It seems that there is a significant difference between the absence of the reflex in the L5 radiculopathy group and the normal group. Electrodiagnostic EDB response is raproducible, and there is a significant difference between latencies for the L5 and normal groups.

REPORT DATE: 06/02/93 WORK UNIT # 9616

DETAIL SUMMARY SHEET

TITLE: Intern Perceptions of Physical Medicine and Rehabilitation

KEYWORDS: physical medicine, perceptions, GME

PRINCIPAL INVESTIGATOR: Braverman, Steven CPT MC
ASSOCIATES: Belandres, Praxedes COL MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine 1991-92 WRAMC Internship Class perceptions of and attitudes toward Physical Medicine and Rehabilitation (PM&R); to explore demographic factors associated with changes in attitude toward PM&R; to determine if perceptions are altered by orientation or routine interactions with the PM&R Service; and to determine the validity of the Leschner 11-item questionnaire used in this study.

TECHNICAL APPROACH
Questionnaires will be given out to the 1991-92 Intern Class at the following four intervals: before and after orientation, 6 months into internship, and at the end of the internship. Questionnaires include the 11-item, 7-point scale originated by Leschner. Statistical analysis will be performed on completed questionnaires as per protocol. Additional questionnaires were distributed to the WRAMC 1992-93 Intern Class before and after their orientation to assess the validity of the questionnaire.

PRIOR AND CURRENT PROGRESS
Data collection was completed July 1992. Fifty-seven of 58 Class of 1991-92 interns completed questionnaires 1 and 2, with about a 25% response rate for questionnaires 3 and 4. Thirty-five of 45 interns in the 1992-93 class returned usable, completed pre- and post-orientation questionnaires. Preliminary data analysis was completed. An abstract was submitted for presentation to the 1993 Annual Meeting of the American Academy of Physical Medicine and Rehabilitation. Acceptance of the abstract is pending.

CONCLUSIONS
The questionnaire was reliable with an alpha reliability of .76. Interns' perceptions of Physical Medicine and Rehabilitation are initially favorable and improve after an orientation.

REPORT DATE: 03/13/93 WORK UNIT # 9617

DETAIL SUMMARY SHEET

TITLE: Use of Topical Capsaicin in Myofascial Pain Syndromes and Primary Fibromyalgia Syndrome

KEYWORDS: substance P, capsaicin, fibromyalgia

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC
ASSOCIATES: Zeigler, Daryl LTC MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To show supporting evidence that topical capsaicin decreases subjective pain intensity when applied over trigger points and tender points in patients with myofascial pain syndrome and fibromyalgia.

TECHNICAL APPROACH
Patients will participate in a 6 week open-labeled pilot study to test the use of 0.025% capsaicin cream on tender and trigger points in the neck and shoulder girdle. Baseline pain measurements will be obtained during the first week of the study with use of the McGill Pain Questionnaire and the visual analogue scale. The cream will then be applied for a 5 week treatment period. The same pain measurement questionnaire and pain relief scale will be used to document changes in subjective pain intensity.

PRIOR AND CURRENT PROGRESS
Twenty-seven patients entered the study. Twenty-five patients completed the study and were included in the analysis. The MANOVA test showed a significant improvement in average scores on the visual analogue scale ($p<.001$) and on the pain relief scale ($p=.006$). Paired t-tests failed to show significant improvement in all pain measurement scores on the McGill Pain Questionnaire. There have been no serious and/or unexpected adverse drug reactions. A manuscript is currently being prepared. Investigators are considering continuing the study in a similar design as a double-blind controlled trial.

CONCLUSIONS
This study demonstrated that 5 weeks of topically applied capsaicin cream can decrease subjective pain intensity when applied over trigger points and tender points in the neck and shoulder region in patients with myofascial pain syndrome and fibromyalgia. Statistically significant improvement was obtained in two primary outcome variables. A double-blind, controlled trial is now necessary to confirm this treatment effect.

REPORT DATE: 03/02/93 WORK UNIT # 9618

DETAIL SUMMARY SHEET

TITLE: Dorsal Scapular Nerve Conduction Studies: An Assessment of Normal Subjects

KEYWORDS: nerve, electrodiagnosis, conduction

PRINCIPAL INVESTIGATOR: Muscari, C Tracy CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To obtain normative data for latencies and amplitudes for the Dorsal Scapular Nerve motor action potential.

TECHNICAL APPROACH
A set distance of 19 cm will be measured from the posterior border of the clavicular insertion of the sternocleidomastoid to the rhomboid area. An electrical stimulus will be given, and the waveform recorded. Latencies and amplitudes will be recorded. Measurements on both right and left sides will be utilized.

PRIOR AND CURRENT PROGRESS
Thirty subjects were evaluated, and data collection has been completed. None of the subjects experienced any adverse reactions or benefited from this study. Statistical analysis has shown that the mean normal latency is 3.7 ms, with a staandard deviation of 0.39 ms. The 95% confidence interval for the mean normal latency is 3.6 ms - 3.8 ms. Side to side comparisons revealed a mean difference of 0.3 ms, and there was not a statistically significant difference between the two sides (p=.33). Amplitudes will be reported but will not be used in statistical analysis due to inaccuracies seen with a needle pickup. An abstract is being prepared to request presentation at a meeting of electrodiagnosticians in New Orleans, LA, October 1993.

CONCLUSIONS
The results may be used to evaluate patients with neuropathies, radiculopathies, and brachial plexopathies.

REPORT DATE: 04/06/93 WORK UNIT # 9619

DETAIL SUMMARY SHEET

TITLE: Strength Training in Short Below-Knee Amputees Using a Modified Isokinetic Exercise System - A Pilot Study

KEYWORDS: isokinetic, amputees, training

PRINCIPAL INVESTIGATOR: Marin, Raul CPT MC
ASSOCIATES: Kishbaugh, David MAJ MC; Kirk, Kevin CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess and document strength gains in the residual limbs of below-knee amputees after isokinetic exercise training using an innovative modification to current isokinetic systems to accommodate for residual limbs.

TECHNICAL APPROACH
The WRAMC Biodex Isokinetic Exercise System was modified by fabricating a lever arm and shin pad to accommodate shorter than usual lower extremity residual limbs. Twelve below-knee amputees (BKS) were to be selected using strict criteria; they were to be pretested at the onset of the training session and again at the completion of the session (3 weeks inpatient). Functional evaluations of gait with the prosthesis were also planned prior to and after the training period by timing the patients as they walked a standard length or distance. Originally, the project was to last 6-8 weeks, and outpatients were to be recruited. This was changed to 3 weeks using inpatients due to inability to recruit outpatients.

PRIOR AND CURRENT PROGRESS
Even after attempts to recruit inpatients for this study (outpatient recruitment was abandoned after it became clear that the amputee clinic did not have enough local BKA's and after approaching the local VA), the study has not progressed beyond the protocol proposal stage. Time constraints as a resident and graduation of the PI this June 1993 prevent continuation of this project.

CONCLUSIONS
Not applicable.

REPORT DATE: 08/13/93 WORK UNIT # 9620

DETAIL SUMMARY SHEET

TITLE: Radiculopathy Screen: Choosing the Most Sensitive Muscles

KEYWORDS: radiculopathy, electromyography

PRINCIPAL INVESTIGATOR: Lauder, Tamara CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the sensitivity of selected groups of muscles to allow quantitative insight into the number of muscles required to identify a radiculopathy of the lumbosacral spine.

TECHNICAL APPROACH
This study is a retrospective chart review of lumbosacral radiculopathy patients diagnosed electrodiagnostically over a 3 year period. All studies fulfilling the inclusion criteria for a radiculopathy will be categorized into specific radiculopathy levels based on review of the literature. Once the studies are categorized, data analysis will be performed utilizing dBase III+ and SPSS/PC+ 3.1 software. The sensitivity of each muscle will be described by the percentage of the presence of abnormal spontaneous activity of each muscle. Sensitivity for each muscle group will be calculated by the percentage of positive radioculopahty screens with a 95% confidence interval.

PRIOR AND CURRENT PROGRESS
A total of 202 charts have been reviewed. Results to date have revealed that the paraspinal muscles alone yielded 81-86% sensitivity. Without paraspinals (PM), two muscle screens yielded 14-34% sensitivity; three muscle screens yielded 56-79% sensitivity, and four muscle screens yielded 77-83% sensitivity. Including PM, four muscle screens yielded 88-96% sensitivity, and five muscle screens yielded 94-98% sensitivity. An 8-11 muscle screen was required to reach 98-100% sensitivity. Further data analysis is in progress, and an article is being written.

CONCLUSIONS
To this point, it appears that four to five muscle radiculopathy screens, including paraspinal muscles, provide acceptable diagnostic sensitivities, minimizing patient discomfort.

REPORT DATE: 09/15/93 WORK UNIT # 9621

DETAIL SUMMARY SHEET

TITLE: High Dose Intravenous Immunoglobulin (IVIG) in the Treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

KEYWORDS: demyelinating disease, immunoglobulin, polyneuropathy

PRINCIPAL INVESTIGATOR: Braverman, Steven CPT MC
ASSOCIATES: Davis, William MAJ MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 1,527 Previous FYs: $ 0 Total: $ 1,527

STUDY OBJECTIVE
To evaluate the clinical and immunologic benefits of high dose intravenous immunoglobulia (IVIG) in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).

TECHNICAL APPROACH
Retrospectic chart review of all patients treated with IVIG through the WRAMC Allergy-Immunology Service who meet diagnostic criteria for CIDP. Pre and post-treatment data will be compared when available for manual muscle testing, isokinetic muscle testing, functional assessment scale, electromyography and nerve conduction velocity studies, and blood immunologic assays for IL2, IL2 receptor, and lymphocyte phenotypes. Statistical analysis will be descriptive in nature with Wilcoxon signed rank test, means, standard deviations, and ranges. Qualitative and quantitative changes in drug therapy will also be presented.

PRIOR AND CURRENT PROGRESS
Retrospective review was completed. Data was collected on six patients; four of whom showed clinical improvement after IVIG treatment. A paper was presented to the American Academy of Physical Medicine and Rehabilitation Annual Assembly, November 1992 and to the Clinical Investigators' Recognition Seminar, March 1993. Pilot study has been completed. Numbers are insufficient to warrant attempt of double-blind, placebo-controlled clinical trial.

CONCLUSIONS
High dose IVIG may be efficacious to some patients in the treatment of CIDP. Further randomized, blinded studies are needed to confirm the variables associated with positive responses to the treatment.

REPORT DATE: 07/12/93 WORK UNIT # 7239

DETAIL SUMMARY SHEET

TITLE: Visual Information Processing in Psychiatric Patients

KEYWORDS: vision, acuity, schizophrenia

PRINCIPAL INVESTIGATOR: Blair, Sidney CAPT MC

DEPARTMENT: Department of Psychiatry STATUS: Completed
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare vernier visual acuity in normal subjects and in psychiatric patients.

TECHNICAL APPROACH
Subjects attempt to discriminate computer-generated vernier stimuli. Responses are tallied and analyzed by computer.

PRIOR AND CURRENT PROGRESS
Prior work evaluated visual stimulus parameters and interaction patterns of visual and auditory stimuli. Current work is directed at instrumentation for presentation of auditory stimuli of varying parameters for the purpose of defining tonal difference thresholds and temporal interference patterns. No new subjects were enrolled in the last year; total enrollment to date is 16. There were no serious or unexpected reactions or subjects withdrawn from the study. There were no benefits to subjects. This study has exceeded the 5-year time limit for a protocol, and is thus terminated.

CONCLUSIONS
No conclusions concerning the original study objective are possible.

REPORT DATE: 03/24/93 WORK UNIT # 7240

DETAIL SUMMARY SHEET

TITLE: Cerebral Dysfunction in Schizophrenic Subtypes

KEYWORDS: schizophrenia, neuropsychology, electrophysiology

PRINCIPAL INVESTIGATOR: Warden, Debra MD
ASSOCIATES: Anderson, Milton CPT MC; Coats, Michael MD

DEPARTMENT: Department of Psychiatry

STATUS: Terminated
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if clinically identified subtypes of schizophrenic patients exhibit findings on neuropsychological and neurophysiological testing consistent with predominantly left hemisphere, right hemisphere, or bilateral frontal lobe dysfunction.

TECHNICAL APPROACH
To identify positive and negative symptom patients by a Positive and Negative Symptom Scale (PANSS) after a semistructured interview. The Schedule for Affective Disorders and Schizophrenia (SADS) will be utilized to confirm the diagnosis of schizophrenia, according to Research Diagnostic Criteria (RDC). Patients will then receive evoked potencial testing, EEG with brainmapping, neuropsychological testing, and neurological exam.

PRIOR AND CURRENT PROGRESS
This research study has been administratively terminated.

CONCLUSIONS
This research study has been administratively terminated.

REPORT DATE: 05/28/93 WORK UNIT # 7245

DETAIL SUMMARY SHEET

TITLE: Investigation of Ultradian Rhythms of Mood in Depression

KEYWORDS: ultradian rhythms, depression, mood variance

PRINCIPAL INVESTIGATOR: Hall, Donald CPT MC
ASSOCIATES: Benedek, David CPT MC; Chang, Audrey PhD

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: May 1991

FUNDING: Current FY: $ 1,092 Previous FYs: $ 163 Total: $ 1,255

STUDY OBJECTIVE
To investigate mood changes within the day.

TECHNICAL APPROACH
Patients will complete a simple questionnaire each hour of the day. Mood scores will be graphed versus time of day, and then the graphs will be analyzed for cycles. The study is unchanged from the original protocol.

PRIOR AND CURRENT PROGRESS
To date, 43 subjects have been entered into this study (none this past year); 38 of these subjects were tested. Mood variance has been quantified for groups (increased in adjustment disorder group). Currently analyzing data for cycles.

CONCLUSIONS
Mood variance is greater in adjustment disorder than in major depression.

REPORT DATE: 09/13/93 WORK UNIT # 7246

DETAIL SUMMARY SHEET

TITLE: A Randomized Concentration-Controlled Trial of Fluoxetine in the Treatment of Major Despressive Disorder

KEYWORDS: fluoxetine, concentration-controlled, depression

PRINCIPAL INVESTIGATOR: Oleshansky, Marvin LTC MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 7,854 Total: $ 7,854

STUDY OBJECTIVE
To demonstrate the relationship between steady-state serum concentrations of the antidepressant fluoxetine (Prozac) and the efficacy of its use in the treatment of outpatients with Major Depressive Disorder (MDD).

TECHNICAL APPROACH
This study is a randomized concentration-controlled clinical trial of Prozac in which dosing is adjusted weekly to achieve a targeted serum fluoxetine concentration. After maintenance of steady-state concentrations of fluoxetine at target levels for 3 weeks, the relationship between the serum concentrations and clinical outcome measures of antidepressant efficacy will be examined.

PRIOR AND CURRENT PROGRESS
To date, five patients have been enrolled in the study (none this past year). Only one patient has completed the protocol. One subject did not meet initial entry criteria, one subject was dropped for a positive urine drug screen, and two subjects did not meet entry criteria because they had signs of improvement in the 1 week placebo lead-in. There were no incidences of serious or unexpected adverse reactions.

CONCLUSIONS
The one subject who finished the protocol demonstrated the feasibility of predicting a patient's steady-state fluoxetine. The problems facing this study are recruiting enough subjects to achieve a large enough n for statistical analysis and reorganizing laboratory support for the analysis of Prozac levels.

REPORT DATE: 07/09/93 WORK UNIT # 7247

DETAIL SUMMARY SHEET

TITLE: Characteristics and Correlates of Outpatient Group Therapy Participants Selected by PGY-3 Psychiatry Residents

KEYWORDS: group therapy, outcome

PRINCIPAL INVESTIGATOR: Cheevers, Tanya LTC MC

DEPARTMENT: Department of Psychiatry STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if specific criteria could predict the outcome of a patient participating in group therapy.

TECHNICAL APPROACH
To obtain data, a questionnaire was specifically designed for the therapists to address specific criteria which they rank for their individual candidates. The questionnaire is given to each patient prior to the first group meeting and after the completion of the group therapy session.

PRIOR AND CURRENT PROGRESS
Research has been completed, and the study is being closed with this report.

CONCLUSIONS
Results indicated that it remains a difficult task for the therapist to subjectively/objectively choose an appropriate group candidate. Factors that we chose which may be predictive of outcome; i.e., motivation, cohesiveness, psychological mindedness, etc., were not statistically significant in predicting outcome. However, this information may stimulate other research to look at closed group therapy at WRAMC.

REPORT DATE: 05/26/93 WORK UNIT # 7248

DETAIL SUMMARY SHEET

TITLE: Psychiatric Diagnoses Included in Medical Discharge Summaries

KEYWORDS: medical discharge, psychiatric diagnoses

PRINCIPAL INVESTIGATOR: Esposito, Maria COL MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine: 1) the percentage of inpatient narrative summaries in which consultations and psychiatric diagnoses are recorded, and 2) whether a specific method of preparing psychiatric consults will result in a higher percentage of inclusion in the narrative summary.

TECHNICAL APPROACH
Charts will be reviewed after the patient is discharged, the narrative summary is prepared, and the chart is finalized by the Patient Administration Directorate (PAD). Charts will be requested from the Medical Records Section of PAD. Psychiatric consultations to be included in the study will be referred via the usual channels. Included/excluded charts will be determined per original protocol.

PRIOR AND CURRENT PROGRESS
During the first year of this study, 181 patient charts were reviewed. A data base has been created, and data entry has begun. All data should be collected by June 1993. When data entry is completed, analysis will be performed.

CONCLUSIONS
Certain demographic factors may describe patient groups whose diagnoses are or are not documented in narrative summaries. Descriptive statistics would be helpful in designing future studies to investigate miscommunication and stigma in the documentation process.

REPORT DATE: 04/13/93 WORK UNIT # 7249

DETAIL SUMMARY SHEET

TITLE: The Art Therapy Assessment of a Criminally Insane Population

KEYWORDS: art, assessment, insane

PRINCIPAL INVESTIGATOR: Lande, Raymond LTC MC
ASSOCIATES: Howie, Paula MA; Chang, Audrey PhD

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To test an art diagnostic assessment tool for potential inclusion as part of the routine forensic psychiatric evaluation of a criminally accused person; and to determine if such an assessment can sufficiently discriminate between two populations matched for psychiatric diagnoses, age, sex, and race. The group variable studies will be the influence, if any, of criminal misconduct.

TECHNICAL APPROACH

The plan is to enroll a minimum of 30 psychiatric patients from Clifton T. Perkins State Hospital Center and the same number of psychiatric patients from Walter Reed Medical Center. The primary focus of this study is to explain the impact of criminal behavior. The primary inclusion factor for enrollment at Clifton T. Perkins would be that the patient has been charged with a crime. The primary exclusion factor for the WRAMC population will be history of arrest. Patients must have AXIS I diagnosis and cannot have only AXIS II diagnosis. Those patients with a diagnosis of substance dependence will be included.

PRIOR AND CURRENT PROGRESS

Eighty study subjects have been enrolled. Experienced art therapists have been trained in the scoring of this specific instrument. Preliminary inter-rater reliability data has been collected. No adverse reactions have been noted. No benefits have occurred to the patients pending further analysis. Following training, eight assessments have been evaluated.

CONCLUSIONS

None so far.

REPORT DATE: 04/14/93 WORK UNIT # 7250

DETAIL SUMMARY SHEET

TITLE: Proto-oncogene Expression in Peripheral Blood Mononuclear Cells in Schizophrenia: A Pilot Study

KEYWORDS: proto-oncogenes, schizophrenia, mononuclear cells

PRINCIPAL INVESTIGATOR: Brown, James CPT MC
ASSOCIATES: Nicholson, Diamuid PhD; Kapur, Janet BA

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 229 Previous FYs: $ 0 Total: $ 229

STUDY OBJECTIVE

To determine if proto-oncogenes are expressed in peripheral blood mononuclear cells of schizophrenics during acute phases of illness.

TECHNICAL APPROACH

Peripheral blood mononuclear cells will be obtained from 30 schizophrenic patients and 2 normal controls. The controls will be used to verify proper experimental method. The DNA isolated from these cells will be probed for altered proto-oncogene expression. A comparison between normal and schizophrenic expression will be performed. These results will be used to test the autoimmune theory of schizophrenia. The assay will be initiated by drawing 30cc of blood from the subject. Mononuclear cells and their genetic material will be isolated by standard procedures. Probes for numerous proto-oncogenes will then be applied. Hybridization will be measured by densitometer.

PRIOR AND CURRENT PROGRESS

To date, cells have been separated from one control and one schizophrenic patient. While practicing technique, it was realized that 30cc of blood will be insufficient. After consultation with experts in the technique, it was determined that 60cc of blood will be necessary. The protocol is now being revised to include this change. There have been no serious or unexpected adverse reactions, no patient benefit, and no patients removed from the study.

CONCLUSIONS

Separation of adequate genetic material from peripheral blood mononuclear cells for proto-oncogene probing will require that more blood be drawn from each subject than originally anticipated. The protocol will proceed after the necessary revision of the consent form.

REPORT DATE: 10/05/93 WORK UNIT # 7251

DETAIL SUMMARY SHEET

TITLE: An Outcome Study of Schizophreniform Disorder Diagnosed at Walter Reed Army Medical Center

KEYWORDS: schizopreniform

PRINCIPAL INVESTIGATOR: Joslin, Scott CPT MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review the diagnostic outcomes of service members medically retired with the diagnosis of Schizophreniform Disorder at Walter Reed Army Medical Center between 1986-1991.

TECHNICAL APPROACH
Questionnaires with cover letters will be mailed to each former service member with consent to study and for collateral contact with their current physician. Data will be collated in PC Plus computer database.

PRIOR AND CURRENT PROGRESS
All (128) patient questionnaires were mailed; to date, 92 have been returned completed. Two hundred and seventy-one questionnaires were sent to their physicians; to date, 140 have been returned.

CONCLUSIONS
Conclusions are provisional. A spectrum of schizophrenic and bipolar outcomes was discovered, and correlation with prognostic features indexed at the time of initial diagnosis is in progress.

REPORT DATE: 12/16/92 WORK UNIT # 9106

DETAIL SUMMARY SHEET

TITLE: Differences in Proportions of Diagnosis Between Ethnic Groups: The Case of Puerto Rican Psychiatric Patients in the Military

KEYWORDS: Hispanic, diagnosis, Puerto Rican

PRINCIPAL INVESTIGATOR: Jones, Franklin MD
ASSOCIATES: Febo, Manuel COL MC; Rothberg, Joseph PhD

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: Dec 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether Hispanic and other minority patients are diagnosed and managed differently from non-minority patients at WRAMC; and to determine whether certain diagnoses are made more commonly in Hispanic patients than other ethnic groups.

TECHNICAL APPROACH

Psychiatric records were reviewed for 2 years with sorting of all Hispanic surnamed patients compared with 100 randomly selected non-Hispanic Caucasian and 100 non-Hispanic Black patients. Demographic and symptom variables will be collected and compared. This study will review all Hispanic surnamed charts, and a random selection of Black and Caucasian patients, for diagnosis and clinical features.

PRIOR AND CURRENT PROGRESS

Study is completed except for analysis. Delay was due to overseas assignment of Dr. Febo. No serious and/or unexpected adverse reactions occurred. amd there were no new developments.

CONCLUSIONS

Island and New York Puerto Ricans appear similar to each other and distinct from Blacks and Caucasians (non-Hispanic) in demographic and clinical features.

REPORT DATE: 12/03/92 WORK UNIT # 4525

DETAIL SUMMARY SHEET

TITLE: Intravenous Administration of I-131-6-B Iodomethylnorcholesterol for Adrenal Evaluation and Imaging

KEYWORDS: adrenal imaging, I-131 NP-59

PRINCIPAL INVESTIGATOR: Anderson, Jay COL MC

DEPARTMENT: Department of Radiology STATUS: Ongoing
APPROVAL DATE: Nov 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To clinically evaluate NP-59 as a diagnostic agent for the detection of cortical disorders. (This radiopharmaceutical is in the category of a Phase III IND). Although these radiopharmaceuticals have been valuable in the evaluation of patients with Cushing's syndrome, primary aldosteronism, and hypoandrogenism, radiopharmaceutical companies do not find it commercially profitable to seek an NDA.

TECHNICAL APPROACH

The technical approach is unchanged. The radiopharmaceutical is obtained from the University of Michigan from Dr. Beierwaltes. The exam is only performed on those patients for whom the primary clinical physician believes potential information could be obtained and outweighs the potential risks. (In order to offer this diagnostic modality to patients, this protocol has been submitted and approved.)

PRIOR AND CURRENT PROGRESS

This radiopharmaceutical remains a valuable diagnostic tool. During the report period, no studies were performed, for a total of 28 patients studied to date. There were no adverse reactions, and no patient has withdrawn. All studies during this period have been clinically useful.

CONCLUSIONS

No conclusion can be made nor are any conclusions anticipated. This is a standard IND to offer a diagnostic exam for patient benefit. In addition, this study saves WRAMC money because the patient is not referred to a civilian hospital to obtain the same exam.

REPORT DATE: 12/03/92 WORK UNIT # 4527

DETAIL SUMMARY SHEET

TITLE: Technetium (Tc99m) Antimony Trisulfide Colloid - A Lymphoscintigraphic Agent

KEYWORDS: lymphoscintigraphy, antimony trisulfide, colloid

PRINCIPAL INVESTIGATOR: Anderson, Jay COL MC

DEPARTMENT: Department of Radiology STATUS: Completed
APPROVAL DATE: Nov 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To clinically evaluate technetium (Tc99m) antimony trisulfide colloid (a Phase III IND radiopharmaceutical) in the evaluation of lymph nodes, lymphatics, and/or bone marrow distribution. Although these agents have been valuable in the evaluation of patients, radiopharmaceutical companies do not find it commercially profitable to seek an NDA. As a result, in order to offer this diagnostic modality to the patients we serve, we must have a protocol.

TECHNICAL APPROACH
The study is unchanged. The pharmaceutical is obtained from Cadema Company and labeled with the routine technetium 99m pertechnetate within our clinic. The exam is only performed on those patients for whom the primary clinical physician believes potential clinical information for the patient may be obtained. Any side effect is recorded on data sheets which are forwarded to the primary commercial company.

PRIOR AND CURRENT PROGRESS
This radiopharmaceutical remains a valuable diagnostic imaging tool. Seven studies were performed during this reporting period, for a total of 457 studies since the protocol started in 1981. The number of studies reported to be effective during this reporting period was seven. No serious or unexpected adverse reactions have been observed.

CONCLUSIONS
This product is no longer available.

REPORT DATE: 09/20/93 WORK UNIT # 4531

DETAIL SUMMARY SHEET

TITLE: Diagnostic Imaging of Adrenal Medulla (Pheochromocytoma, Paragangliomas, and Neuroblastomas) with I-131 MIBG (Metaiodobenzylguanidine Sulfate)

KEYWORDS: pheochromocytoma, I-131 MIBG

PRINCIPAL INVESTIGATOR: Rodriguez, Ana COL MC

DEPARTMENT: Department of Radiology STATUS: Completed
APPROVAL DATE: Sep 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the use of I-131 metaiodobenzylguanidine sulfate (I-131 MIBG) as an aid in the diagnosis, evaluation, and localization of pheochromocytomas, paragangliomas, neuroblastomas, and/or adrenal medullary hyperplasia. This radiopharmaceutical has already been proven useful in the evaluation of disease noted above. Because no commercial company pursues approval by the FDA, it remains in an IND status. To reduce cost, an IND was obtained from the FDA to offer this scan.

TECHNICAL APPROACH

This protocol will offer a diagnostic exam for the patient rather than implement a scientific study; no experimental design compilation of data, etc., will be done. All side effects will be reported to the FDA. There is no modification to the original protocol.

PRIOR AND CURRENT PROGRESS

During the past reporting period, five patients had I-131 MIBG studies performed. This makes a total of 77 patients since the protocol started in 1984. There have been no adverse reactions, and no patients have withdrawn. Of the five patients patients injected during this report period, all five studies were clinically useful. However, this drug no longer needs an IND protocol. It has been released for commercial use.

CONCLUSIONS

No conclusion can be made nor are any conclusions anticipated. This was a standard IND to offer a diagnostic exam for patient benefit.

REPORT DATE: 09/07/93 WORK UNIT # 4535

DETAIL SUMMARY SHEET

TITLE: Pharyngeal and Esophageal Manifestations of Rheumatoid Arthritis

KEYWORDS: rheumatoid arthritis, esophagus

PRINCIPAL INVESTIGATOR: Kohanski, Phillip CPT MC
ASSOCIATES: Dachman, Abraham MD

DEPARTMENT: Department of Radiology STATUS: Completed
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain if there is a relationship between rheumatoid arthritis and esophageal disease. Similar diseases, such as scleroderma, are believed to have esophageal disease associated with them.

TECHNICAL APPROACH
Questionnaires, brief histories, and physicals are performed to see if a patient has rheumatoid arthritis. Barium swallows are performed to see if the patient has esophageal disease. These two sets of data are then compared.

PRIOR AND CURRENT PROGRESS
A total of 20 patients and 25 controls were enrolled in this study; none this past year. Patient enrollment is complete.

CONCLUSIONS
No conclusions have been made at this time.

REPORT DATE: 10/08/93 WORK UNIT # 4538

DETAIL SUMMARY SHEET

TITLE: Ultrasound Guided Laser Ablation of Tumors

KEYWORDS: laser, liver, ultrasound

PRINCIPAL INVESTIGATOR: Dachman, Abraham MD

DEPARTMENT: Department of Radiology STATUS: Terminated
APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 500 Total: $ 500

STUDY OBJECTIVE
To employ an experimental technique to treat colorectal metastases limited to the liver. This is to be considered a palliative procedure that avoids the need for surgery or general anesthesia.

TECHNICAL APPROACH
Patients with limited colorectal carcinoma metastases to the liver, and not candidates for surgery, are staged using CT and ultrasound. Under ultrasound guidance, a needle is placed into the tumor and the laser fiber is placed through the needle into the tumor. An Nd:YAG laser is used at 1 to 3 watts for about 6 minutes. Sequential placement of the laser fiber in various portions of the tumor are used to attempt to totally destroy the tumor.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 05/04/93 WORK UNIT # 4700

DETAIL SUMMARY SHEET

TITLE: CT Evaluation of Postoperatie Pneumoperitoneum

KEYWORDS: pneumoperitoneum, computed tomography

PRINCIPAL INVESTIGATOR: Earls, James CPT MC
ASSOCIATES: Colon, Edgar MD; Garrett, Meredith CPT MC

DEPARTMENT: Department of Radiology

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 251 Previous FYs: $ 0 Total: $ 251

STUDY OBJECTIVE
To evaluate the rate of resorption of pneumoperitoneum in postoperative patients, comparing the sensitivity of computed tomography (CT) to the left lateral decubitus film.

TECHNICAL APPROACH
Prospectively perform CT scans and left lateral decubitus films on patients following uncomplicated abdominal surgery; postoperative days 3 and 6. The studies will be evaluated in a blinded fashion for the presence, location, and volume of free air.

PRIOR AND CURRENT PROGRESS
A total of 27 CT scans and 27 left lateral decubitus films were obtained from 17 patients. Fifteen patients were studied on postoperative day 3, and 12 were studied on postoperative day 6. Pneumoperitoneum was identified in 13/15 (87%) of the CT scans and 8/15 (53%) of the plain films on postoperative day 3, and in 6/12 (50%) of the CT scans and 1/12 (8.4%) of the plain films on postoperative day 6. Only 9 of 19 patients (46%) with free air identified on CT demonstrated pneumoperitoneum on the left lateral decubitus exam.

CONCLUSIONS
The left lateral decubitus examination is less sensitive than generally thought. CT was significantly more sensitive ($p=.004$) than the plain film in detecting small amounts of free intraperitoneal air. The incidence of pneumoperitoneum in the postoperative period as detected by CT is greater than that previously reported. Two new preferential spaces have been described, the pararectus and midrectus recesses, for collection of small amounts of free air on CT.

REPORT DATE: 06/11/93 WORK UNIT # 4701

DETAIL SUMMARY SHEET

TITLE: CT Directed Needle Localization of Peripheral Pulmonary Nodules Prior to Thoracoscopic Resection

KEYWORDS: computed tomography, pulmonary nodule, biopsy

PRINCIPAL INVESTIGATOR: Earls, James CPT MC
ASSOCIATES: McAdams, H. Page CPT MC; Colon, Edgar MD

DEPARTMENT: Department of Radiology

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a new technique to enable resection of peripherally based pulmonary nodules by thoracoscopy.

TECHNICAL APPROACH
On occasion, a patient will require open thoracotomy for pathologic diagnosis of a pulmonary nodule if prior attempts at endoscopic or transthoracic needle biopsy are unsuccessful. By placing a localization needle into or near the nodule, it can then be removed by thoracoscopy, a much less invasive procedure, with less morbidity and mortality than open thoracotomy.

PRIOR AND CURRENT PROGRESS
A localization needle was placed in eight patients undergoing thoracoscopy to date (five female, three male, average age 48.8 years). Thoracoscopic resection was successful in seven patients; one patient required open thoracotomy because thoracoscopic resection was technically unfeasible. No unexpected or serious adverse reactions have been reported.

CONCLUSIONS
CT guided needle localization of pulmonary nodules prior to thoracoscopic resection appears to be a technically feasible procedure.

REPORT DATE: 09/16/93 WORK UNIT # 4702

DETAIL SUMMARY SHEET

TITLE: Imaging in Congenital Hypercoagulable Disorders

KEYWORDS: hypercoagulable states, Computed tomography

PRINCIPAL INVESTIGATOR: Earls, James CPT MC
ASSOCIATES: McAdams, H. Page MAJ MC; Colon, Edgar MD

DEPARTMENT: Department of Radiology

STATUS: Completed
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 934 Previous FYs: $ 0 Total: $ 934

STUDY OBJECTIVE
To demonstrate the range of imaging findings in patients with congenital hypercoagulable states; and to compile an educational "pictorial essay" based on these disorders.

TECHNICAL APPROACH
The imaging files of patients with a confirmed diagnosis of either protein C, protein S, or antihrombin III deficiency will be reviewed retrospectively.

PRIOR AND CURRENT PROGRESS
A total of 34 imaging files were reviewed. Of these, 26 patients with protein S, 4 with protein C, and 4 with antithrombin III deficiency were identified. Patients experienced vascular thrombosis involving the deep venous system of the upper and lower extremities, portal, splenic, mesenteric, jugular, and iliac veins. The patients suffered arterial thrombi in the central nervous system distribution. No imaging findings that were specific for the disorders could be identified.

CONCLUSIONS
Patients with congenital hypercoagulable states most commonly suffer deep venous thrombosis of the lower extremities and pulmonary embolism. No imaging findings that are specific for the disorder were identified. Recurrent thrombosis is common and complicates diagnostic imaging. Caval interruption is frequently required.

REPORT DATE: 06/09/93 WORK UNIT # 2032A

DETAIL SUMMARY SHEET

TITLE: Pain Control After Thoracotomy and Its Effect on Pulmonary Function

KEYWORDS: pain, thoracotomy, pulmonary function

PRINCIPAL INVESTIGATOR: Lupkas, Raymond CPT MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare three different methods of pain control after thoracotomy and to evaluate the effects on pulmonary function.

TECHNICAL APPROACH
Patients are randomized to receive epidural morphine, intercostal nerve blocks, or interpleural local anesthetic for postoperative pain control. Patients are visited daily for 3 days and asked to perform a bedside pulmonary function test and to quantitate their pain using a visual analog pain scale. The original protocol has been modified to eliminate the interpleural local anesthetic group because it was found that this group did not receive adequate pain control.

PRIOR AND CURRENT PROGRESS
This research study has been administratively terminated.

CONCLUSIONS
This research study has been administratively terminated.

REPORT DATE: 10/28/92 WORK UNIT # 2045A

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of the Davol Intraspinal Port

KEYWORDS: epidural, narcoti :, cancer pain

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Epidural catheters are being used with more frequency to relieve cancer pain in the terminally ill patient. Thus, this protocol will study the placement of permanent epidural catheters with intraspinal ports for the relief of cancer pain.

TECHNICAL APPROACH
A videotape, "The Placement of Davol Permanent Epidural Catheters," has been created, which is 15 minutes long and describes the technique of pl ement of the catheter. FDA trials are being conducted for these intraspinal ports.

PRIOR AND CURRENT PROGRESS
Eleven patients have been enrolled; the last one completed the study in January 1990. All of these patients have died secondary to their primary disease. The study is ongoing and waiting the modification of the port by the company.

CONCLUSIONS
No conclusions can be reached at this point. Further study is needed.

REPORT DATE: 03/05/93 WORK UNIT # 2050A

DETAIL SUMMARY SHEET

TITLE: Intraoperative Use of Patient Controlled Anxiolysis

KEYWORDS: patient-controlled, analgesia, stress response

PRINCIPAL INVESTIGATOR: Furukawa, Kenneth MAJ MC
ASSOCIATES: Baum, Andrew PhD

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the effect of intraoperative use of a patient-controlled analgesia device for anxiolysis, provided the patient has adequate analgesia for the operation with a subarachnoid block. Is there a difference compared to standard anesthetist-administered anxiolysis?

TECHNICAL APPROACH

All patients will be given a subarachnoid anesthetic for comparable operative procedures; inguinal herniorrhapies or knee arthroscopies. Preoperative evaluation includes psychometric testing, blood and urine samples for fentanyl and cortisol, repetitive fine motor testing, and extensive counselling. Intraoperative evaluation includes all of the above before skin incision and at skin closure. Postoperative visits repeat the preoperative measures. Analysis of questionnaires and laboratory samples is performed at the Uniformed Services University of the Health Sciences.

PRIOR AND CURRENT PROGRESS

A total of 22 patients have completed the study protocol. During the past year, only two of four patients were completed due to a lack of psychologist interest in this protocol. Unfortunately, funding for serum and blood testing did not materialize. Most importantly, several studies in the Anesthesiology literature have studied this clinical question and have concluded that little or no difference exists between the different routes of anxiolysis.

CONCLUSIONS

No significant difference in anxiolysis scoring was found between patient-administered and anesthetist-administered anxiolysis.

REPORT DATE: 04/27/93 WORK UNIT # 2051A

DETAIL SUMMARY SHEET

TITLE: Perioperative Myocardial Ischemia or Infarction During and Following Noncardiac Surgery in Patients who have Undergone Previous Coronary Artery Bypass Graft or Percutaneous Transluminal Coronary Artery Surgery

KEYWORDS: myocardial ischemia, myocardial infarction, hemodynamic responses

PRINCIPAL INVESTIGATOR: Kline, Mark CPT MC
ASSOCIATES: Guzzi, Louis MAJ MC; Stoltzfus, Daniel MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To record and compare the hemodynamic responses and the incidence of myocardial ischemia or infarction during and following non-cardiac surgery in patients who have undergone previous percutaneous transluminal coronary artery (PTCA) surgery with those in whom previous coronary artery bypass grafting (CABG) has been performed.

TECHNICAL APPROACH

Essentially, intraoperative hemodynamic responses will be compared, as well as postoperative ischemia episodes, as documented by Holter monitoring, EKG recordings, and cardioenzymes drawn each postoperative day for a maximum of 3 days.

PRIOR AND CURRENT PROGRESS

To date, 37 of the projected 50 patients have been enrolled (5 this past year). There have been no serious or unexpected adverse reactions, and no patient has been withdrawn from the study. Presently, no patient has required acute interventional management as a result of the monitoring.

CONCLUSIONS

Study is still in progress.

REPORT DATE: 02/04/93 WORK UNIT # 2054A

DETAIL SUMMARY SHEET

TITLE: The Effect of theh Sprotte Atraumatic 24 Gauge Spinal Needle on the Incidence of Postdural Puncture Headache

KEYWORDS: Sprotte needle, post dural puncture, headache

PRINCIPAL INVESTIGATOR: Carvill, Kathleen LTC NC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of post dural puncture headache with the 24 gauge Sprotte needle as compared with 25 gauge conventional spinal needles in surgical patients.

TECHNICAL APPROACH
A convenient sample of 100 patients will be randomly assigned to either the Sprotte needle experimental group or to the 25 gauge needle control group. Patients will be assessed postoperatively for the occurrence of postdural puncture headache.

PRIOR AND CURRENT PROGRESS
At present, a sample of 60 patients has been achieved; 8 this past fiscal year. Since 100 patients has been identified as the desired sample size, data collection is still in progress. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Study is still in progress. Data collection and analysis is not complete.

REPORT DATE: 10/27/92 WORK UNIT # 2056A

DETAIL SUMMARY SHEET

TITLE: Development of Ultra Long Duration Local Anesthetic Agents in a Rat Model

KEYWORDS: local anesthetic, ultra long, rat

PRINCIPAL INVESTIGATOR: Kline, Mark MAJ MC
ASSOCIATES: Lojeski, Edwin CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $23,113 Previous FYs: $ 0 Total: $ 23,113

STUDY OBJECTIVE

To develop and evaluate ultra-long duration local anesthetics in a rat model. A wide variety of local anesthetics are to be prepared as lecithin-coated microcrystals in an attempt to prolong their duration of action. Agents will be tested for their ability to provide both peripheral neural blockade and major conduction blockade. This study also attempts to evaluate the tissue toxicity of the agents tested.

TECHNICAL APPROACH

The primary screening test for local anesthetic duration will involve performing an intradermal tail block in the rat and monitoring response to a tail clamp assay. Response to major conduction blockade will also be monitored with the tail clamp assay. Tissue toxicity of the test agents will be evaluated by placing the test agent intradermally (next to the sciatic nerve) or in the subarachnoid space. Tissues from euthanized rats will then be evaluated by light and electron microscopy for evidence of toxic effects.

PRIOR AND CURRENT PROGRESS

Sixty-eight rats have been used. Prior and current progress includes demonstrating that lecithin-coated tetracaine microcrystals can provide anesthesia of 43 horus duration to the rat tail. This compares to a tail block duration of 8 hours when standard tetracaine formulations are used. This data was presented in abstract form at the 1992 American Society of Anesthesiologists' Annual Meeting. The results also demonstrated that lecithin-coated tetracaine microcrystals cause minimal inflammation when placed intradermally. This data was also presented in abstract form at the American Society of Anesthesiologists' 1992 Annual Meeting.

CONCLUSIONS

Lecithin-coated tetracaine microcrystals are capable of providing ultra-long duration local anesthesia, and microcrystal technology appears to be a promising method of prolonging local anesthetic action. Further toxicity testing, as well as testing of additional local anesthetic agents, will be required.

REPORT DATE: 02/09/93 WORK UNIT # 2057A

DETAIL SUMMARY SHEET

TITLE: Epidural Clonidi e for the Treatment of Pain Associated with Advanced Cancer

KEYWORDS: epidural, clonidine, cancer

PRINCIPAL INVESTIGATOR: Kline, Mark CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the use of central access clonidine for the treatment of cancer pain.

TECHNICAL APPROACH
This is a multicenter study. Patients will have epidural catheters placed and receive morphine or morphine and clonidine. The patients will rate pain relief and sedation during the trial period.

PRIOR AND CURRENT PROGRESS
By the time this protocol was approved, the sponsoring company had collected enough patients to complete the study.

CONCLUSIONS
The results of the study done by the company showed that epidural clonidine works.

REPORT DATE: 10/28/92 WORK UNIT # 2058A

DETAIL SUMMARY SHEET

TITLE: The Effect of Anesthesia and Surgery on Patients with Mildly Elevated Liver Enzymes

KEYWORDS: liver enzymes, anesthesia

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study patients with mildly elevated liver enzymes to see what effect, if any, anesthesia and surgery have on these patients.

TECHNICAL APPROACH
After baseline enzymes are obtained, liver enzymes will be obtained at the time of surgery, and at 3 days, 1 week, and 3 months after surgery.

PRIOR AND CURRENT PROGRESS
Due to personnel constraints, data collection has not begun on this study.

CONCLUSIONS
None.

REPORT DATE: 11/19/92 WORK UNIT # 2059A

DETAIL SUMMARY SHEET

TITLE: CIBA-GEIGY Protocol 1900-Use of Intravenous Ismelin in Patients with Reflex Sympathetic Dystrophy, Causalgia or Raynaud's Phenomenon/Disease Amendment II

KEYWORDS: guanethidine, pain

PRINCIPAL INVESTIGATOR: Phillips, William MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the effects of intravenous regional guanethidine on pain resulting from reflex sympathetic dystrophy.

TECHNICAL APPROACH
Guanethidine will be administered by the Bier technique to patients with sympathetically mediated pain.

PRIOR AND CURRENT PROGRESS
This study has been closed because of denial of FDA approval. No patients were enrolled in this study.

CONCLUSIONS
None.

REPORT DATE: 01/26/93 WORK UNIT # 2061A

DETAIL SUMMARY SHEET

TITLE: Medtronic Model 3885 PISCES-Delta Lead for Spinal Cord Stimulation

KEYWORDS: spinal, cord, stimulation

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the stability of the Pisces-Delta lead in the epidural space. The stimulation pattern of the electrode will be monitored over time.

TECHNICAL APPROACH
The Pisces-Delta will be placed in the epidural space, and placement will be confirmed with flat plate radiographs. Patients will be followed over the course of the next 2 years with serial examination and radiographs to determine if there is any migration of the lead.

PRIOR AND CURRENT PROGRESS
To date, this protocol has not been approved. Awaiting submission of liability statement from Medtronics.

CONCLUSIONS
None.

REPORT DATE: 01/21/93 WORK UNIT # 2062A

DETAIL SUMMARY SHEET

TITLE: Dose-Response for Glycopyrolate in Infant and Children Anesthetized with Halothane and Nitrous Oxide

KEYWORDS: glycopyrolate, dose-response

PRINCIPAL INVESTIGATOR: Lupkas, Raymond MAJ MC
ASSOCIATES: Greaser, Raymond CPT MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if there is a dose-response relationship for glycopyrolate after a standard inhalation induction in the pediatric patient.

TECHNICAL APPROACH
The anesthesiologist is randomized to give his/her standard dose of glycopyrolate after and inhalation induction in the ASA I/II patient. Heart rate, blood pressure, and electrocardiac determinations are made.

PRIOR AND CURRENT PROGRESS
This research study has been administratively terminated.

CONCLUSIONS
This research study has been administratively terminated.

REPORT DATE: 01/14/93 WORK UNIT # 2063A

DETAIL SUMMARY SHEET

TITLE: Normothermic vs. Hypothermic Cardiopulmonary Bypass: The Stress Response with Varying Sufentanil Doses

KEYWORDS: stress hormone production, cardiopulmonary bypass

PRINCIPAL INVESTIGATOR: Bolt, Stephen CPT MC
ASSOCIATES: Phillips, William MAJ MC; Edwards, Fred COL MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $31,313 Previous FYs: $ 0 Total: $ 31,313

STUDY OBJECTIVE

To determine if stress hormone production varies during two different types of cardiopulmonary bypass, when a standardized dose of narcotic anesthesia is administered to each patient.

TECHNICAL APPROACH

This study is a non-blinded, prospective, randomized trial. Each patient undergoes preoperative and postoperative neuropsychological testing. During the surgery, six blood samples of 10 cc each are obtained at specified times. Various physiologic parameters are recorded at each sample time. The blood is analyzed for sufentanil, epinephrine, norepinephrine, and cortisol levels. Statistical analysis is performed via ANOVA.

PRIOR AND CURRENT PROGRESS

To date, 44 of 90 patients are enrolled; 2 patients were withdrawn due to surgical considerations. Analysis of the blood is time consuming, and much of the data is, as yet, unavailable. Currently, no trends have been identified in hormonal/narcotic levels. Likewise, no trends have been identified yet in the neuropsychological testing in order for the testing to remain unbiased. No serious and/or unexpected adverse reactions have been noted to date. No direct patient benefit has been identified to date as a result of this work.

CONCLUSIONS

No conclusions on this work are currently available.

REPORT DATE: 02/08/93 WORK UNIT # 2064A

DETAIL SUMMARY SHEET

TITLE: A Study of the Effect of Acadesine on Adverse Cardiac Outcomes in Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery

KEYWORDS: Acadesine, cardiac outcomes

PRINCIPAL INVESTIGATOR: Fontana, John CPT MC
ASSOCIATES: Yee, Lawrence CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To collect perioperative data which will determine whether Acadesine may have an effect on adverse cardiac outcomes following coronary artery bypass graft (CABG).

TECHNICAL APPROACH
This multi-center study is a prospective, randomized, double-blind, placebo-controlled, parallel group protocol. The study involves the perioperative administration of Acadesine, an agent which appears to have protective effects against myocardial ischemia and cardiac arrhythmias. Clinical outcomes will be assessed to determine whether Acadesine may have beneficial effects on patients undergoing CABG surgery.

PRIOR AND CURRENT PROGRESS
This protocol was approved locally in February 1992. However, in April 1992 the study sponsor notified the investigators that the patient accrual goal had been met. Thus, the protocol was not forwarded to HSC. In October 1992, the study sponsor reopened accrual to strengthen the statistical significance of their data. No new safety concerns had been raised, and the protocol is currently being reviewed by HSC. The total number of patients seen study-wide is 630 in the U.S.A. and 825 in Europe. No incidence of serious and/or unexpected adverse reactions has been reported.

CONCLUSIONS
No specific conclusions have been drawn at this time. Additional data will need to be collected from the participating centers.

REPORT DATE: 03/14/93 WORK UNIT # 2065A

DETAIL SUMMARY SHEET

TITLE: Intraoperative Utilization and Effect on Brain Relaxation

KEYWORDS: diuretic, neurosurgery, intracranial pressure

PRINCIPAL INVESTIGATOR: Bettencourt, Joesph MAJ MC
ASSOCIATES: Gordon, Jeff CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the osmotic diuretic mannitol is as effective in raising the serum osmolality by 10 mOsm as the combination of mannitol and the loop diuretic furosemide.

TECHNICAL APPROACH
Volunteers are randomized by surgeon to either a mannitol only group or a mannitol and furosemide group. Serum osmolality is followed, and the drugs are titrated to achieve an increase of 10 mOsm in the serum osmolality. The surgeon's opinion of brain relaxation on a scale of 1-5 is also recorded.

PRIOR AND CURRENT PROGRESS
At this time, 16 patients have been enrolled in the study. The plan calls for 50 patients to be enrolled. Investigators hope to increase the rate of patient enrollment and complete the study.

CONCLUSIONS
None.

REPORT DATE: 05/18/93 WORK UNIT # 2066A

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of Perioperative Ischemia Research Group - Cardiac Surgery Epidemiologic Database (McSPI-CSEDB)

KEYWORDS myocardial infarction, CABG

PRINCIPAL INVESTIGATOR Yee, Lawrence CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: May 1992

FUNDING: Current FY $ 0 Previous FYs: $ 0 Total $ 0

STUDY OBJECTIVE
To collect basic information on the incidence of myocardial infarction and adverse cardiac outcome following coronary artery bypass graft (CABG) surgery

TECHNICAL APPROACH
This multi-center study involves the prospective collection of preoperative demographic information, intraoperative anesthetic and surgical data, as well as detailed postoperative follow-up outcome data This data, obtained from chart reviews, will be filed into a comprehensive data base

PRIOR AND CURRENT PROGRESS
A total of 2,400 patients has been enrolled, no patients from WRAMC. Data collection continues nationwide, and it is anticipated that WRAMC will enroll patients during the coming year There has been no incidence of serious or unexpected adverse reactions No specific benefit to patients is expected as a result of participating in this study.

CONCLUSIONS
No specific conclusions have been drawn Additional data will need to be collected from the participating centers

REPORT DATE 06/30/93 WORK UNIT # 2067A

DETAIL SUMMARY SHEET

TITLE Fiberoptically Assisted Intravenous Catheter Placement

KEYWORDS fiberoptic device, intravenous catheter

PRINCIPAL INVESTIGATOR Matson, Michael LTC MC

DEPARTMENT Department of Surgery STATUS Ongoing
SERVICE Anesthesia Operative Service APPROVAL DATE Jun 1992

FUNDING Current FY $ 0 Previous FYs $ 0 Total $

STUDY OBJECTIVE
To assess the utility of a fiberoptic device in facilitating the placement of intravenous catheters

TECHNICAL APPROACH
One hundred adult patients presenting for surgery that require two intravenous catheters will be enrolled into the study. One catheter will be placed using the standard technique, and one will be placed using the fiberoptic system

PRIOR AND CURRENT PROGRESS
No patients have been enrolled into this study, to date, due to manufacturing delays.

CONCLUSIONS
None.

REPORT DATE: 08 3 WORK UNIT # 2068A

DETAIL SUMMARY SHEET

TITLE: Comparison of the Hemodynamic Stability of General Endotracheal Anesthesia Combined with Epidural Local Anesthesia Versus General Endotracheal Anesthesia Combined with Epidural Narcotic in Patients Undergoing Radical Prostatectomy

KEYWORDS: henmodynamic stability, prostatectomy, anesthesia

PRINCIPAL INVESTIGATOR: Froelich, Edward CPT MC

DEPARTMENT: Department of Surge[illegible] STATUS: Completed
SERVICE: Anesthesia-Operati[illegible]ice APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 revious FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the hemodynamic stability of general endotracheal anesthesia combined with epidural local anesthesia versus general endotracheal anesthesia combined with epidural narcotic in patients undergoing radical prostatectomy.

TECHNICAL APPROACH
Patients will be randomized to receive endotracheal anesthesia combined with: (1) epidural local anesthesia; or (2) epidural narcotic. Both hemodynamic and anesthetic requirements will be compared between the two groups.

PRIOR AND CURRENT PROGRESS
This study was submitted to the U.S. Army Research and Development Command for funding. Notification was received in January 1993 that due to overall budget constraints this study would not be funded.

CONCLUSIONS
Not applicable.

REPORT DATE: 06/07/93 WORK UNIT # 2504

DETAIL SUMMARY SHEET

TITLE: The Effect of Speech Babble on the Speech Recognition Ability of Soldiers with H-3 Physical Profiles

KEYWORDS: hearing-impaired, speech perception, noise

PRINCIPAL INVESTIGATOR: Cord, Mary MA
ASSOCIATES: Atack, Rodney PhD; Walden, Brian PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 8,181 Previous FYs: $ 1,119 Total: $ 9,300

STUDY OBJECTIVE

To develop and standardize a measure of speech recognition ability in noise to be administered to soldiers who are being evaluated by the Military Medical Retention Boards (MMRB) for possible administrative action. Such a measure will permit more objective judgements regarding relative communication handicap.

TECHNICAL APPROACH

The study will have two stages. The first experiment is designed to determine the least favorable signal-to-noise ratio (S/N) for monosyllabic words and multi-talker noise at which normal-hearing listeners can just maintain 100% correct recognition of words. In the second experiment, the speech and noise task will be presented to a large sample of H-3 profile soldiers at that S/N to derive normative data for this task.

PRIOR AND CURRENT PROGRESS

Data collection on 15 normal-hearing subjects was completed, and a S/N for experiment two was determined. Data was collected on 323 H-3 profile soldiers at 11 Army Audiology facilities. Test-retest data was collected on 20 subjects. Normative data, in the form of percentile rankings, was derived so that individual soldiers' performance cna be compared to that of the large sample distribution. Test tapes and instructions for administration have been distributed to all Army audiologists. There have been no serious or unexpected adverse reactions, and no subjects have withdrawn from the study. There has been no direct benefit to patients.

CONCLUSIONS

As hypothesized, scores varied considerably from near 100% correct to relatively poor recognition. Test-retest data indicated that this is a reliable measure. Army audiologists are now using this measure to make recommendations to the MMRB regarding soldiers' potential communication handicaps.

REPORT DATE: 11/10/92 WORK UNIT # 2508

DETAIL SUMMARY SHEET

TITLE: Auditory Supplements to Speechreading

KEYWORDS: auditory-visual, speech perception, hearing-impaired

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To serve as a grant proposal submitted to the NIH to obtain funding. The goal of the grant is to delineate more fully how auditory and visual cues are combined in bisensory speech perception by hearing-impaired subjects. Three factors assumed to be important for AV performance will be studied. These are the subject's ability to 1) identify consonants, 2) integrate auditory and visual cues, and 3) use context.

TECHNICAL APPROACH
Each of the proposed experiments will include measures of auditory, visual, and auditory-visual identification of speech tokens. Both segmental and connected speech materials will be used. To avoid AV ceiling effects, the auditory signals will be degraded with noise, by filtering, or both. Confusion matrices and overall performance levels on the various experimental tasks will be used as predictors of overall AV benefit for individual subjects.

PRIOR AND CURRENT PROGRESS
This grant is now in its second year of funding from NIH. Laboratory facilities to control auditory and visual speech stimuli have been developed. A study relating to the first project on the grant has recently been completed (W.U.# 2511), and results from 30 normal hearing subjects were presented at the Acoustical Society meeting in November 1992. Data collection in a second study (W.U.# 2514) has begun, and subjects are being recruited.

CONCLUSIONS
Each experiment proposed in this grant will be carried out under its own work unit number. Descriptions of progress and the use of human subjects will be submitted individually for each project.

REPORT DATE: 01/11/93 WORK UNIT # 2510

DETAIL SUMMARY SHEET

TITLE: Prediction of Stuttering Severity from Physiologic Measures of Speech Motor Systems

KEYWORDS: stuttering, speech kinematics, severity

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES: Rock, Donna MA; Cord, Mary MA

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 73 Previous FYs: $ 0 Total: $ 73

STUDY OBJECTIVE

To evaluate the association between stuttering severity and kinematic measures of lip, jaw, and laryngeal movements obtained during fluent and disfluent productions of simple speech utterances. A related goal is to carry out a taxonomic description of disfluency types based on orofacial and laryngeal movement.

TECHNICAL APPROACH

Structural displacements of the upper lip, lower lip, and jaw will be recorded with a head-mounted strain gauge transducer system. Vocal fold vibration will be recorded with an electroglottograph, which transduces tissue impedance. These physiologic signals will be digitized at 500 Hz and acquired in 4-sec epochs associated with each speech utterance. Computer-based cursor-controlled measures will be obtained off-line on movement timing, displacement, and velocity. Measures of stuttering severity will be derived from percentage counts of words disfluent as assessed in videotape recordings taken as part of clinical assessments.

PRIOR AND CURRENT PROGRESS

Since the last progress report, speech kinematic and stuttering severity data have been obtained on 12 additional stutterer subjects, bringing the total to 34. Analysis of the kinematic data has been completed on 17 of the 34 subjects. There have been no serious and/or unexpected adverse reactions, and none of the subjects have withdrawn from the study. There has been no benefit to patients.

CONCLUSIONS

Kinematic analysis of lip, jaw, and laryngeal movements warrant two tentative conclusions. First, more severe stutterers show reduced variability in relative timing measures obtained across different structures, particularly for inter-structural timing of lip versus larynx and jaw versus larynx. Recent models of speech control and stuttering make this prediction. A second conclusion is that speech therapy conditions increased durations of inter- and intrastructural timing.

REPORT DATE: 04/12/93 WORK UNIT # 2511

DETAIL SUMMARY SHEET

TITLE: The Transmission of Prosodic Information Via Selected Spectral Regions of Speech

KEYWORDS: speech perception, normal-hearing, prosody

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD
ASSOCIATES: Cord, Mary MS

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 1,067 Previous FYs: $ 5,350 Total: $ 6,417

STUDY OBJECTIVE

To determine a) whether prosodic speechy information (e.g., syllable number, syllabic stress, sentence intonation, and phrase juncture) can be equally conveyed by different, but equally intelligible, spectral regions of speech; and b) whether suprasegmental cues are mapped spectrally in the same way as overall speech intelligibility.

TECHNICAL APPROACH

This protocol includes three sub-projects, each with 10 normal-hearing adult subjects. Depending on the sub-project, subjects will listen to filtered words or sentences and will be required to identify either a) the number of syllables and the stress pattern of the word, b) the intonation (rising for a question, falling for a statement) of the sentence, or c) the phrase structure of a sentence. For each sub-project, six filter conditions will be evaluated. The filter conditions chosen will have the same Articulation Index (AI=0.1) according to ANSI Standard S3.5-1969 and the same intelligibility (roughly 35% correct monosyllabic word identification).

PRIOR AND CURRENT PROGRESS

Data collection for all three sub-projects (the transmission of syllable number and syllabic stress in 1-3 syllable words, intonation in sentences, and rhythmic structure in short phrases) has been completed. A total of 30 normal-hearing subjects were tested; 5 this past fiscal year. There have been no adverse or unexpected reactions from subjects, and no subjects have withdrawn from this study. Aside from general information and monetary compensation, there have been no benfits to the subjects participating in this protocol.

CONCLUSIONS

Results indicate that prosodic cues are generally available throughout the speech spectrum. However, some subjects have difficulty extracting intonation and phrase-boundary cues from the high-frequency bands. We suspect that these subjects would benefit from training. The broad distribution of these cues across different frequency regions is likely to be of substantial benefit to speechreading.

REPORT DATE: 08/03/93 WORK UNIT # 2514

DETAIL SUMMARY SHEET

TITLE: Evaluating the Articulation Index for Auditory-Visual Consonant Recognition

KEYWORDS: speech perception, normal-hearing, articulation index

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D.
ASSOCIATES: Cord, Mary MS; Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 3,540 Previous FYs: $ 0 Total: $ 3,540

STUDY OBJECTIVE

To identify the most salient auditory cues in auditory-visual consonant recognition, and to examine the accuracy of the Articulation Index procedure for predicting auditory-visual speech recognition scores from auditory speech recognition scores.

TECHNICAL APPROACH

This protocol includes two sub-projects requiring normal-hearing subjects to identify via speechreading (V), audition (A), and combination of the two (AV), 18 initial consonants distorted by noise (sub-project 1) or filtering (sub-project 2). In sub-project 1, eight different speech-to-noise ratios resulting in A scores between 40-90% correct are evaluated. In sub-project 2, 12 different filter conditions resulting in a similar range of percent correct scores are evaluated.

PRIOR AND CURRENT PROGRESS

Data collection for the two sub-projects (A, V, and AV consonant perception in noise, and A, V, and AV consonant perception under conditions of bandpass filtering) has been completed. A total of 12 normal-hearing subjects were tested; 10 this past year. There have been no adverse or unexpected reactions from subjects who have completed or withdrawn from this study. Aside from general information and monetary compensation, there has been no benefit to the subjects participating in this protocol.

CONCLUSIONS

Auditory conditions having the same overall intelligibility (same Articulation Index) do not necessarily result in the same auditory-visual intelligibility, and low-frequency bands of speech tend to provide more benefit to speechreading than high-frequency bands of speech. These data are well predicted by models of auditory and visual cue-redundancy, indicating the current ANSI (1969) procedure for predicting speechreading benefit is inadequate for consonant recognition.

REPORT DATE: 10/06/92 WORK UNIT # 2515

DETAIL SUMMARY SHEET

TITLE: Frequency Resolution and the Detection of Spectral Contrast

KEYWORDS: frequency resolution, hearing-impaired, speech perception

PRINCIPAL INVESTIGATOR: Leek, Marjorie Ph.D.
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 240 Previous FYs: $ 910 Total: $ 1,150

STUDY OBJECTIVE

To evaluate the relationship between the loss in contrast between peaks and valleys in the speech spectrum after cochlear processing and the reduction in frequency resolution in hearing-impaired listeners. People with sensorineural hearing loss often have difficulty understanding speech, especially in noisy environments. This may be due in part to a flattening of the peaks and valleys in the speech spectrum caused by reduced frequency resolution accompanying hearing loss.

TECHNICAL APPROACH

Spectral contrast remaining in the post-cochlear internal representation of sounds will be measured by having listeners discriminate a sound with a sinusoidal change in amplitude across the spectrum (rippled spectrum) from a sound with a flat spectrum. The amplitude of spectral change needed for detection will be determined as a function of spacing of the peaks and valleys in the spectra. This function is determined by the spacing of the peaks and the frequency resolution ability of the listener. Independent measures of frequency resolution also will be made. Correlations between discrimination performance and frequency resolution measures will be evaluated.

PRIOR AND CURRENT PROGRESS

Data collection is complete on this project, and data analysis has begun. Preliminary results suggest that hearing-impaired listeners require greater amplitude differences between peaks and valleys of complex spectra than do normal-hearing listeners in order to discriminate a flat from a peaked spectrum. Further, the hearing-impaired subjects' best discimination performance spanned a wider range of ripple frequencies than normal, probably as a result of their poorer-than-normal frequency resolution. Five normal-hearing and five hearing-impaired subjects have completed the study. There have been no adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

The results of this study suggest that, in the analysis of speech sounds by impaired ears, spectral peaks become flattened and formant spacing may be more ambiguous. Both of these alterations are probably a consequence of the reduced frequency resolution demonstrated by these patients. The result of this processing may be a distorted internal representation of some speech sounds after cochler analysis.

REPORT DATE: 10/15/92 WORK UNIT # 2516

DETAIL SUMMARY SHEET

TITLE: Orofacial Force Control and Acoustics of Speech Production in Adult Dysarthria Patients

KEYWORDS: adult dysarthria, orofacial force control, acoustic analyses

PRINCIPAL INVESTIGATOR: Thompson, Patryce MA
ASSOCIATES: McClean, Michael PhD; Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 1,235 Previous FYs: $ 80 Total: $ 1,315

STUDY OBJECTIVE

To determine whether nonspeech measures of oromotor performance are correlated with and predictive of the level of speech motor deficit in dysarthric subjects.

TECHNICAL APPROACH

This study will test the fine force control of the lips, tongue, and jaw, and obtain acoustic measures of speech sound production in dysarthric adults. Specialized force transducers and computer software will be used to record and analyze dysarthric subjects' ability to match static force levels with lips, tongue, and jaw. Acoustic analysis of speech will involve computer processing of several productions of /p/ and /t/ consonants. The statistical moments of the amplitude spectra will be used in a discriminant analysis of the two consonants.

PRIOR AND CURRENT PROGRESS

To date, the force analysis procedure has been completed on 10 normal and 4 dysarthric subjects. Acoustic analysis has been completed on nine normal and five dysarthric speakers. Insufficient numbers of dysarthric subjects preclude a correlation analysis at this time. However, considerable progress has been made in instrumentation set-up, learning new techniques for physical analysis, and developing new clinical test procedures. There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

Both the force and acoustic analysis procedures provided important information on the orofacial control and speech production capabilities of each dysarthric subject. Continued acquisition of these types of data should effectively address the initial question.

REPORT DATE: 11/02/92 WORK UNIT # 2518

DETAIL SUMMARY SHEET

TITLE: Prespeech Modulation of Lip Muscle Reflexes in Stutterers and Nonstutterers

KEYWORDS: speech, reflexes, stuttering

PRINCIPAL INVESTIGATOR: McClean, Michael Ph.D.

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 90 Previous FYs: $ 0 Total: $ 90

STUDY OBJECTIVE

To determine whether stutterers and nonstutterers differ in how lip muscle reflexes are modulated during their preparation to speak, and whether reflex modulation is influenced by the speech sound being produced. After work began on this study it became apparent that a test procedure was needed to show consistent reflex modulation effects among the normal subjects.

TECHNICAL APPROACH

EMG recordings are made of reflex and voluntary activity in upper and lower lip muscles. A pulsatile mechanical stretch is given to the mouth's right corner using a servo-control linear motor; this serves as both a reaction time and reflex stimulus. On each trial the EMG and stimulus signals are digitized and saved in computer files for analysis. On every other trial a line on an oscilloscope cues the instruction to say a simple word starting with "p" as soon as the subject feels the mechanical stretch. A no-response trial follows at a fixed interval of 2-4 sec. Software is used to calculate the mean levels of the EMG signals over specified pre- and poststimulus time intervals.

PRIOR AND CURRENT PROGRESS

In the first year, several pilot studies were required before consistent performance was obtained in normal subjects. The test procedures have now been run twice on four normal subjects. In each subject, a significant reduction in reflex response levels has been noted in the speech condition, with the basic effect being more prominent in the second experimental run. Reflex suppression effects have been most consistently observed in the early reflex component, which has a latency of about 15 ms. As expected, reflex response levels vary systematically with prestimulus EMG and background force. Reflex amplitudes are still quite variable within experimental conditions. This should be reduced with an improved head positioner to achieve more stable lip coupling with the stimulator. Ten subjects have been run in the past year, with no serious or unexpected adverse reactions and no benefit to subjects.

CONCLUSIONS

The consistency of the basic experimental effect is encouraging and suggests that in the coming year it will be feasible to undertake similar testing on adult stutterer subjects. The functional significance of the suppressed reflex responses is uncertain. Additional testing in which the voluntary response is varied will be carried out in the coming year to partially address this issue.

REPORT DATE: 01/11/93 WORK UNIT # 2519

DETAIL SUMMARY SHEET

TITLE: Computer Modeling and Analysis of Lip Muscle Activation for Speech

KEYWORDS: computer modeling, speech, neuromotor control

PRINCIPAL INVESTIGATOR: McClean, Michael Ph.D.
ASSOCIATES: Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 546 Previous FYs: $ 0 Total: $ 546

STUDY OBJECTIVE

To develop a computer model of neural processes which are likely to underlie muscle activation of a single muscle system for speech motor control. To accomplish this, the activation patterns of lip muscle single motor units during speech production will be described.

TECHNICAL APPROACH

Computer software will be developed which has the capability for interconnection and realistic modeling of several neurons. Neurons are to be modeled as single integrator response functions. EMG and displacement signals from the lip muscle system will be acquired and analyzed with computer. These data along with relevant animal neurophysiologic data will be used to constrain simulated neural circuits intended to model neural systems involved in speech production.

PRIOR AND CURRENT PROGRESS

During the first year of this research, the essential features of the intended computer software for simulation of neuron population has been completed. Numerous simulations of different circuits have been carried out, including possible circuits for pattern generation in speech. Recording and signal acquisition procedures for the project have been fully developed, and preliminary data have been obtained on one subject. There have been no serious or unexpected adverse reactions. No patients have withdrawn from the study or received benefit from participation.

CONCLUSIONS

Simulations of motoneuron recruitment and modulation of trigeminal-facial reflexes support the validity and heuristic value of the model.

REPORT DATE: 05/04/93 WORK UNIT # 2520

DETAIL SUMMARY SHEET

TITLE: Comparison of Linear and K-Amp Hearing Aid Fi tings by Experienced Hearing Aid Users

KEYWORDS: hearing aid, trial period, preferred

PRINCIPAL INVESTIGATOR: Surr, Rauna MS
ASSOCIATES: Cord, Mary MA; Walden, Brian PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 1,910 Previous FYs: $ 0 Total: $ 1,910

STUDY OBJECTIVE

To determine whether the benefits provided by Linear Class D and K-Amp hearing aid circuitries differ from each other in routine clinical evaluation and in real-life listening environments.

TECHNICAL APPROACH

Binaural Linear Class D and K-Amp hearing aids will be custom ordered for patients who need replacements for old hearing aids. A two-period cross-over design will be used. The circuitry to be evaluated first will be randomized across subjects. Clinical evaluation will consist of real ear insertion response (REIR) measures using four input levels. A 30-day trial period will follow. The patients will complete a hearing aid benefit questionnaire (PHAB) after each trial. After both trial periods, the patients will retain the circuitry they prefer.

PRIOR AND CURRENT PROGRESS

All 18 patients have been enrolled, and the data has been collected. Most of the data analyses have been done. A poster on this study was presented at the Annual Convention of the American Academy of Audiology, Phoenix, AX, in April 1993. The plan is to write a manuscript for publication.

CONCLUSIONS

REIR results indicate that the two circuitries are comparable with 65 dB input levels, but differ with higher input levels. Preference is evenly divided between the two circuitries. PHAB results show no overall difference across subjects but tend to yield higher subscale scores for the preferred circuitry.

REPORT DATE 05 14 93 WORK UNIT # 2521

DETAIL SUMMARY SHEET

TITLE Spectral Contrast Perception and the Internal Signal-To-Noise Ration in Hearing-Impaired Listeners

KEYWORDS spectrum, hearing loss, noise

PRINCIPAL INVESTIGATOR Leek, Marjorie PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: May 1992

FUNDING: Current FY: $ 2,236 Previous FYs: $ 0 Total: $ 2,236

STUDY OBJECTIVE
To ascertain the relative importance of two sequelae of impaired frequency resolution in hearing-impaired patients. Individuals with hearing loss often complain of difficulty understanding speech in noisy environments. Poor frequency resolution, often accompanying sensitivity loss in these patients, produces a smearing of the peaks and valleys in speech spectra, as well as a reduced signal-to-noise ratio within processing channels in the cochlea.

TECHNICAL APPROACH
Using highly schematized vowel-like sounds, the amount of contrast between spectral peaks and valleys required for vowel identification will be measured in quiet and in three levels of background noise. Susceptibility to increased noise will be inferred by comparing peak-to-valley differences for equal identification performance at each noise level. Frequency resolution will be measured using a notched-noise masking procedure at two center frequencies. This procedure provides estimates of bandwidth and asymmetry of internal auditory filters within individuals. The results from the identification experiment will be interpreted in light of the degree of impairment in frequency resolution within individuals.

PRIOR AND CURRENT PROGRESS
A total of 15 subjects have been enrolled; one withdrew before completing the study (no reason given), and two were unable to perform the auditory identification task and were excused. Data have been collected on six hearing-impaired and six normal-hearing subjects. Preliminary analysis suggests that patients with poor frequency resolution at 2000 Hz require greater than normal spectral contrast for stimulus identification to offset the effectd of listening in noise. However, group differences in overall performance between normal-hearing and hearing-impaired subjects were smaller than expected from previous studies. There have been no serious or unexpected adverse reactions. There is no benefit to the subjects.

CONCLUSIONS
Study results suggest that for both normal-hearing and hearing-impaired listeners, an increase in noise in the listening environment must be accompanied by increased contrast in spectral peaks and valleys of these vowel-like stimuli in order for stimulus identification to be maintained. This general effect of noise is exaggerated when frequency resolution is impaired due to damage to the cochlea.

REPORT DATE: 08/10/93 WORK UNIT # 2588

DETAIL SUMMARY SHEET

TITLE: Hearing Loss and the Perception of Complex Sounds

KEYWORDS: resolution, harmonics, spectral

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 4,031 Total: $ 4,031

STUDY OBJECTIVE

This work unit is a grant proposal submitted to the National Institutes of Health to obtain funding. The goal of the grant is to determine how the impaired spectral and temporal processing accompanying sensorineural hearing loss interferes with the identification and dis .imination of speech-like sounds. The proposal includes seven studies, each of which will be submitted for approval as a separate protocol.

TECHNICAL APPROACH

Each of the proposed experiments includes measurements of frequency resolution and a measure of the internal representation of harmonic complexes. Frequency resolution will be assessed using a notched-noise threshold procedure which allows the tracing of the internal auditory filter. Measures of temporal and spectral processing of harmonic complexes will be made by asking subjects to identify sounds which are constructed to have some of the acoustic characteristics of speech. Confusions among selected stimuli will indicate the degree of impairment of the internal representations of those sounds, which will then be related to the measures of frequency resolution.

PRIOR AND CURRENT PROGRESS

During the past year, data collection and preliminary data analysis have been completed on three experiments, and pilot work is underway on one other. Twenty-one patients have participated in protocols associated with this grant this year, for a total enrollment to date of 118 subjects. There have been no serious or unexpected adverse reactions. Three patients did not complete one of the studies, due to unwillingness or inability to perform the perceptual task. There is no direct benefit to patients.

CONCLUSIONS

Each experiment proposed in this grant is carried out under its own work unit number. Descriptions of progress and the use of human subjects is submitted individually for each project.

REPORT DATE 01 15 93 WORK UNIT # 2590

DETAIL SUMMARY SHEET

TITLE: Modeling Impaired Frequency Resolution in Normal Ears

KEYWORDS: hearing loss, frequency resolution, auditory models

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 8,768 Previous FYs: $ 6,560 Total: 15,328

STUDY OBJECTIVE

To determine the feasibility of using signal processing of speech-like sounds to simulate the impaired cochlear processing found in individuals with sensorineural hearing loss. Successful simulation of hearing impairment may lead subsequently to a method for compensating for these impaired processing mechanisms.

TECHNICAL APPROACH

A computer model of impaired cochlear processing is being developed with parameters based on audiological measures from individual subjects. Three subjects with hearing loss will act as "templates" for testing the model. Measurements of frequency resolution are made and entered as parameters into the model. The subjects will then identify sets of vowel-like sounds, producing confusion matrices that reflect the pattern of perceptual distortions they experience. Confusion matrices obtained from normal subjects for the stimulus set processed through the model will be compared to results from the impaired subjects to assess the accuracy of the simulation of hearing loss.

PRIOR AND CURRENT PROGRESS

Work during this year has focused on generating appropriate vowel-like stimuli through the computer's cochlear model and setting up the experimental paradigm on the laboratory computer. A triadic comparison method will be used to generate similarity matrices among the processed stimuli. The stimuli are modeled after three different patterns of frequency resolution obtained from three hearing-impaired listeners. In addition to these stimuli for this study, the "impaired" model has been used to generate hypotheses concerning other experiments in this laboratory. No new vowel recognition data have been collected during this year. Three hearing-imnpaired subjects had previously participated in this experiment. There have been no adverse reactions, and no subjects have been withdrawn from the study. There is no benefit to the subject.

CONCLUSIONS

The computer model in use in this laboratory has been shown to be responsive to specific functional aspects of cochlear lesions, producing outputs that may reflect the distorted speech perception observed in hearing-impaired individuals. These computer-distorted speech stimuli demonstrate a qualitative similarity to the hypothesized perceptions of patients suffering from hearing loss. Quantitative measures to evaluate this similarity will be made this year.

REPORT DATE: 02/02/93 WORK UNIT # 2591

DETAIL SUMMARY SHEET

TITLE: Nonlinear Cochlear Processing in Normal Hearing and Hearing Impaired Listeners

KEYWORDS: spectral contrast, phase, compressive nonlinearity

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 970 Previous FYs: $ 2,785 Total: $ 3,755

STUDY OBJECTIVE

To demonstrate the benefit to vowel identification hypothesized to occur due to a compressive nonlinearity in normal cochlear processing, and to determine whether that benefit is preserved in patients with sensorineural hearing loss.

TECHNICAL APPROACH

An internal enhancement of spectral peaks due to cochlear processing will allow good vowel discrimination even if the actual peaks have reduced amplitude. In a three-alternative forced choice task, listeners are asked to discriminate between /u/ (duke) and /oo/ (book) with the amount of spectral peak-to-valley contrast varying from 1 to 10 dB The stimuli are presented at either a high or low intensity, and the phase relationships among the spectral components of a sound are controlled to produce either a very peaky or a very flat waveform. A comparison of performance across the intensity and phase conditions will permit assessment of the function of the cochlear nonlinearity.

PRIOR AND CURRENT PROGRESS

Data analysis is complete, and a manuscript describing this study is currently under review for publication. No new patients have been enrolled since the last annual report. The total number of subjects enrolled in the study is 19. There have been no serious or adverse reactions from subjects, nor has any subject withdrawn. There is no benefit to the subjects.

CONCLUSIONS

For normal-hearing subjects, there is a small but consistent enhancement of spectral contrast in harmonic complexes with peaked waveforms at high intensities, suggestive of nonlinear cochlear processing. Hearing-impaired listeners do not, as a group, provide evidence for nonlinear processing of these waveforms at high levels. Signal processing to increase the spectral contrast in speech might improve speech recognition for these patients.

REPORT DATE: 05/04/93 WORK UNIT # 2594

DETAIL SUMMARY SHEET

TITLE: Measurement of Ear Canal Sound Pressure Levels in Infants and Young Children

KEYWORDS: hearing aids, ear canal SPL, infant

PRINCIPAL INVESTIGATOR: MacNeil, Donna MA

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Army Audiology and Speech Center APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 6,220 Total: $ 6,220

STUDY OBJECTIVE
To develop a clinically practical procedure for predicting sound pressure levels (SPL) developed in the ear canal when hearing aids are worn by very young children. Correction factors from test cavities to real-ear measurements in infants and young children will enable hearing aid output levels to be set to a level which will provide maximum gain without overamplification which could cause additional hearing loss.

TECHNICAL APPROACH
Difficulties in enlisting pediatric subjects, and recent data published by Feigin et al. (1989) which casts doubt on the relation between ear canal volume and SPL measures, has prompted re-thinking of our original goals and procedure. By examining the relationship between ear canal volume and real-ear SPL for 14 patients who completed the protocol, as well as in simulated ear volumes, the investigator feels that the sought-after relation can be obtained without the need for additional patients. Both graphical and correlational technique will be used for this purpose.

PRIOR AND CURRENT PROGRESS
Fourteen subjects have been enrolled altogether (none this past year). There has been no incidence of serious or unexpected adverse reactions. It was expected that the children in this study would demonstrate greater real ear to coupler differences than would adults. A recent study by Lewis and Stelmachowicz, entitled "Real Ear to 6-cm^3 Coupler Differences in Young Children," published in JSHR, February 1993 has shown that by 2 years of age these differences are similar for adults and children. Test-retest information in children under age 2 was considered unreliable, due to activity level and probe tube movement. Due to these findings, the study should be terminated. Progress to date does not warrant continuation.

CONCLUSIONS
This study should be closed.

REPORT DATE: 02/02/93 WORK UNIT # 2598

DETAIL SUMMARY SHEET

TITLE: Frequency Resolution on Hearing Impaired and Noise Masked Normal Hearing Listeners

KEYWORDS: frequency resolution, hearing-impaired, masking

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 750 Previous FYs: $ 1,995 Total: $ 2,745

STUDY OBJECTIVE

To determine whether the loss in frequency resolution often experienced by hearing-impaired listeners is directly related to their reduced sensitivity, and therefore might be simulated with noise masking in normal-hearing subjects, or whether a separate auditory pathology independent of elevated thresholds coexists in these patients.

TECHNICAL APPROACH

Frequency resolution in two frequency regions will be measured in normal-hearing and hearing-impaired subjects under conditions of quiet and two broadband noise masking conditions. Characteristics of the auditory filters derived from these measurements were determined to allow a comparison of both bandwidth and asymmetry of the filters across subject groups and within subjects as their sensitivity was decreased by the broadband noise floor.

PRIOR AND CURRENT PROGRESS

Data analysis is complete on this study, and a manuscript has been submitted for publication. A second manuscript is anticipated after further analysis of these data to examine the additivity of masking in normal-hearing and hearing-impaired persons and to determine the appropriateness of treating hearing-impairment as an internal masker. No additional subjects have participated in this study during this year. A total of 10 subjects have completed the study. There have been no serious or adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

Auditory filter bandwidths and asymmetries increase with continuous broadband noise in both normal-hearing and hearing-impaired subjects, especially at a center frequency of 2000 Hz. However, factors other than frequency resolution, i.e., i.e., suppression, may underlie filter estimates for normal-hearing subjects under masking conditions. Auditory filter shapes for hearing-impaired subjects are not well-modeled as resulting from the presence of an internal noise masker.

REPORT DATE: 02/05/93 WORK UNIT # 2060A

DETAIL SUMMARY SHEET

TITLE: The Relationship Between Right Ventilator Volume by Thermodilation Catheter and Left Ventilator Volume by Transesophageal Echo-Cardiography

KEYWORDS: volume, transesophageal, echocardiography

PRINCIPAL INVESTIGATOR: Stoltzfus, Daniel MAJ MC
ASSOCIATES: Thwaites, Brian CPT MC; Vernalis, Marian LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To measure the correlation of right ventricular end-diastolic volume (RVEDV) (thermodilution), pulmonay artery pressures (PAD/PCWP) (Swan-Ganz catheter), and left ventricular end-diastolic volume (LVEDV) during cardiopulmonary bypass.

TECHNICAL APPROACH

Patients scheduled for elective cardiopulmonary bypass grafting (CABG) procedures will have hemodynamic monitor, to include a pulmonary artery catheter (REF-1) and a transesophageal echocardiograph (TEE). At five time points during surgery, measurements will be made of RVEDVI, PAD, PCWP and CVP. Simultaneously short axis images of the left ventricle will be recorded for "off-line" calculation of LVEDVI.

PRIOR AND CURRENT PROGRESS

To date, data collection has occurred for 24 patients. No additional patients will be enrolled. Analysis has begun on the TEE recordings for calculation of LVEDVI. The data base has been created, and data entry is near completion.

CONCLUSIONS

Pending completion of the data base and statisical analysis.

REPORT DATE: 02/10/93 WORK UNIT # 3008

DETAIL SUMMARY SHEET

TITLE: The Use of Capnography During the Transport of Intubated Patients

KEYWORDS: capnography, transport, critically ill

PRINCIPAL INVESTIGATOR: Stoltzfus, Daniel MAJ MC
ASSOCIATES: Kuzma, Paul CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 5,571 Total: $ 5,571

STUDY OBJECTIVE

To evaluate the information gained from a non-invasive measure of exhaled carbon dioxide while transporting mechanically ventilated, critically ill patients. Also, to evaluate if the use of this device would better ensure adequate patient ventilation.

TECHNICAL APPROACH

A baseline measure (prior to transport) of the patient's minute ventilation arterial blood gas, peak airway pressure, and exhaled carbon dioxide concentration will be compared to the values obtained following transport out of the ICU to a second location. During the transport back to the ICU, the nurse or doctor will be instructed to maintain a set number (baseline while on the ventilator) of exhaled CO2. There has been no modification to the original protocol.

PRIOR AND CURRENT PROGRESS

A total of 15 subjects have been enrolled in the study; none this past year. There have been no serious or unexpected adverse reactions, and no patients have withdrawn from the study. The difference in the efficiency of manual ventilation and arterial chemistries when capnography was added during intrahospital transport was observed. The mean decrease in the patient's arterial pH during "blinded transport" was .10 compared to .037 with the use of capnography. The mean increase in arterial pCO2 during "blinded transport" was 13.3 mm Hg, compared to 5.1 mm Hg when capnography was used. Both met statistical significance (p=.003 and .0005, respectively). The study is completed and was terminated early because of an ethical concern for patient safety.

CONCLUSIONS

The conclusion is that without capnography subjects develop acidemic states which might be harmful. Patients are normally ventilated in a more efficient and safer fashion when capnography is used.

REPORT DATE: 03/12/93 WORK UNIT # 3009

DETAIL SUMMARY SHEET

TITLE: Effect of Empiric Low Dose Amphotericin B on the Development of Disseminated Candidiasis in a Surgical Intensive Care Unit

KEYWORDS: low-dose, amphotericin B, candidiasis

PRINCIPAL INVESTIGATOR: Whatmore, Douglas LTC MC
ASSOCIATES: Aronson, Naomi LTC MC; Longer, Charles LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if amphotericin B in low dose (0.3 mg/kg opposed to standard dose of 0.5-1.0 mg/kg) used empirically early in a critically ill patient's course will prevent the dissemination of Candida infections.

TECHNICAL APPROACH

The study will be prospective, randomized, and single-blinded (to the patient/family), with patients receiving low-dose amphotericin B or nothing after obtaining informed consent. Entrance criteria include persistent evidence of sepsis for less than 96 (originally 120) hours on antibiotics, multi-organ system failure involving two organ systems with evidence of Candida at one site (originally did not require evidence of Candida), or Candida isolated from two sites. Evidence of disseminated candidiasis precludes enrollment due to the need for standard dose regimens.

PRIOR AND CURRENT PROGRESS

Five subjects were enrolled since the last report; bringing the total enrollment to 24. One patient completed the protocol, and two patients were discharged to floor prior to completion of study data. One patient died on day 6. One patient was removed from the study with three positive fungal cultures and was placed on full dose amphotericin. No subject has had any serious or unexpected adverse reaction.

CONCLUSIONS

The study will continue until at least 30 subjects have been enrolled (15 in each group). To date, no conclusions may be reached regarding the potential benefit of early use of low dose amphotericin B to prevent dissemination of fungal disease.

REPORT DATE: 01/12/93 WORK UNIT # 3012

DETAIL SUMMARY SHEET

TITLE: Work of Breathing as a Predictor of Failure to Wean from Mechanical Ventilation in Patients with Severe Chronic Obstructive Pulmonary Disease (COPD)

KEYWORDS: work of breathing, mechanical ventilation, COPD

PRINCIPAL INVESTIGATOR: Low, Lewis CPT MC
ASSOCIATES: Harrington, Gerald LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine in patients with severe chronic obstructive pulmonary disease (COPD) if there is a difference in work of breathing (WOB) between those who tolerate removal from mechanical ventilation and those who require reintubation.

TECHNICAL APPROACH

An adult patient with COPD, who has required mechanical ventilation for greater than 24 hours, and who is ready (per the primary care team) for extubation, is identified. The patient's WOB is determined via the metabolic cart. The primary team is blinded to the results. The patient is extubated and followed for 24 hours. WOB levels in those patients who tolerate extubation will be compared with those who fail it. The requirement for informed consent was waived because the study only involves the prospective collection of exhaled gas, does not alter the standard of care, and involves no risk to the patient.

PRIOR AND CURRENT PROGRESS

Metabolic cart for use in this and other protocols was obtained in FY92.. (Funds were from another protocol.) Proficiency with the cart has been achieved. No patients have been enrolled.

CONCLUSIONS

Due to the decrease in ICU patients secondary to budgetary concerns, the potential patient pool has decreased. The researchers will continue to watch for and study eligible patients, but the study may require more time than was initially anticipated.

REPORT DATE: 06/09/93 WORK UNIT # 3013

DETAIL SUMMARY SHEET

TITLE: The Effect of Arterial Lines on the Amount of Blood and the Number of Blood Test Drawn From Patients

KEYWORDS: arterial line, blood draws, blood tests

PRINCIPAL INVESTIGATOR: Low, Lewis CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Critical Care Medicine Service APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the presence or absence of an arterial line effects the amount of blood, the number of blood tests, and the number of blood drawing procedures on patients.

TECHNICAL APPROACH
All adults with APACHE scores of 9-20 will be divided into two groups based upon whether they do or do not have an arterial line. They will be followed for 48 hours, and during this time, the above objectives will be measured. Patients will be disqualified if they have a central line or have an arterial line placed or removed after the study begins.

PRIOR AND CURRENT PROGRESS
The target goal of 50 subjects has been met. There have been no serious or unexpected adverse reactions. Data collection and analysis is completed. Manuscript preparation for submission for publication is in progress.

CONCLUSIONS
The presence of an arterial line increased the number of blood tests, phlebotomy procedures, and amount of blood drawn from patients in the ICU by 26-49%. This leads to increased costs, infection risk, and blood loss.

REPORT DATE: 02/02/93 WORK UNIT # 2035

DETAIL SUMMARY SHEET

TITLE: Investigation of the Etiology of Postoperative Hypocalcemia after Thyroidectomy in the Thyrotoxic Patient

KEYWORDS: surgery, thyroid, hypocalcemia

PRINCIPAL INVESTIGATOR: Azarow, Kenneth CPT MC
ASSOCIATES: Beam, Thomas LTC MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: General Surgery Service APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the thyrotoxic individual is more susceptible to hypocalcemia following thyroid surgery than is the euthyroid patient.

TECHNICAL APPROACH
Patients are evaluated in clinic preoperatively; blood is drawn for all parameters mentioned in the study. Twenty-four hour urine is obtained. Postoperative blood draws are performed by the surgical team and handled by the Principal Investigator. Patients are followed per normal post-surgical routine by the operating surgeon.

PRIOR AND CURRENT PROGRESS
Although three control patients were entered on this study by the original PI, Dr. Azarow, no further work has been accomplished, and this study should be closed.

CONCLUSIONS
None.

REPORT DATE: 11/11/92 WORK UNIT # 2060

DETAIL SUMMARY SHEET

TITLE: Gastrointestinal Involvement in Wegener's Granulomatosis

KEYWORDS: Wegener's granulomatosis

PRINCIPAL INVESTIGATOR: Jaques, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: General Surgery Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To detail the unusual gastrointestinal involvement in Wegener's granulomatosis.

TECHNICAL APPROACH
Case review, review of slides, review of literature, and preparation of scientific paper for submission.

PRIOR AND CURRENT PROGRESS
This project has been completed. A paper has been written and submitted for publication.

CONCLUSIONS
Case report; unique care provided.

REPORT DATE: 05/04/93 WORK UNIT # 2317

DETAIL SUMMARY SHEET

TITLE: Intraocular Irrigating Solutions: Effect on Corneal Endothelium

KEYWORDS: endothelial cells, cornea, glutathione

PRINCIPAL INVESTIGATOR: Kramer, Kenyon COL MC
ASSOCIATES: Puckett, Ted CPT MC; Miller, Michael MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Ophthalmology Service

STATUS: Completed
APPROVAL DATE: Apr 1983

FUNDING: Current FY: $ 675 Previous FYs: $ 0 Total: $ 675

STUDY OBJECTIVE

To determine the relative importance of glutathione in intraocular irrigating solutions to the corneal endothelium during cataract surgery.

TECHNICAL APPROACH

Preoperative cell size measurements and corneal thickness measurements will be made. Subjects will randomly receive intraocular irrigating solutions with glutathione or without. Similar measurements will be made postoperatively and compared.

PRIOR AND CURRENT PROGRESS

Initially, 51 patients were studied with insufficiently conclusive results, An additional 67 patients have been studied this past fiscal year (118 altogether). There was no statistically significant difference between these solutions in their effects on corneal endothelium following extracapsular cataract surgery. MANOVA analysis was used with a power of .8. There were no serious or unexpected adverse effects.

CONCLUSIONS

Locally prepared dextrose bicarbonate lactated Ringer's solution at $10/500 ml was equally effective on extracapsular cataract surgery as a more expensive ($55/500 ml) commercial glutathione containing solution.

REPORT DATE: 01/11/93 WORK UNIT # 2318

DETAIL SUMMARY SHEET

TITLE: The Effects Upon Ocular Structures of Optical Polycarbonate and of Various Eye Protective Substances Applied to and Incorporated Within It

KEYWORDS: polycarbonate, ocular eye, intraocular

PRINCIPAL INVESTIGATOR: Wertz, Fleming COL MC
ASSOCIATES: Ward, Thomas MAJ MC; Cavallaro, Brian CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Ophthalmology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 8,882 Previous FYs: $ 0 Total: $ 8,882

STUDY OBJECTIVE

To determine the ocular toxicity, if any, of polycarbonate lenses and various dyes applied to or incorporated within the lenses. Polycarbonate lenses are being issued as eye protection to soldiers. It is anticipated that some of these protective lenses will shatter in combat and that fragments of the lens will be driven into the eye.

TECHNICAL APPROACH

Fragments (0.4 mg) of BLPS lenses and frontserts will be surgically implanted into eyes of albino rabbits. The animals will be randomized into six groups: clear polycarbonate lens, tinted polycarbonate lens, 2 wavelength protective frontsert, 3 wavelength protective frontsert, iron (positive control), and sham operated eyes (negative control). The animals will be given clinical exams, including intraocular pressure and bright-flash ERG's, prior to both fragment implantation and enucleation. The animals will be euthanized at 1, 2, 4, and 26 weeks. An interim clinical exam will be performed at 12 weeks on the 26 week animals. The enucleated eyes will be examined and sectioned for histopathologic evaluation.

PRIOR AND CURRENT PROGRESS

Those eyes implanted with 3 wavelength frontsert fragments exhibited supernormal dark-adapted ERG b-wave amplitudes when compared to sham operated eyes at 2 weeks ($p<0.05$). Anterior chamber flare and vitrious cell were significantly greater at early time points (</=2 weeks) in the eyes implanted with 3 wavelength frontsert fragments when compared to negative controls ($p's<0.05$). Six animals have been used this fiscal year; 149 have been used altogether.

CONCLUSIONS

A reliable and reproducible system for evaluating the intraocular toxicites of ballistic and laser protective eyewear has been developed. The apparent early toxicity of the BLPS 3 alpha frontsert fragments warrants high medical evacuation priority and urgent vitrectomy in cases of accidental intraocular implantation.

REPORT DATE: 01/11/93 WORK UNIT # 2319

DETAIL SUMMARY SHEET

TITLE: The Efficacy of Cyanoacrylates in the Primary Closure of Conjunctival Scleral Lacerations

KEYWORDS: cyanoacrylate, scleral, laceration

PRINCIPAL INVESTIGATOR: Wertz, Fleming COL MC
ASSOCIATES: Ward, Thomas MAJ MC; Cavallaro, Brian CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Ophthalmology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 3,905 Previous FYs: $ 9,915 Total: $ 13,820

STUDY OBJECTIVE

To determine whether scleral lacerations can be effectively closed in New Zealand white rabbits using cyanoacrylate glue, and to determine the ocular toxicity, if any, of the glue. Currently, scleral lacerations are sutured. This is a time-consuming procedure, and it is anticipated that in combat, O.R. time will be of short supply. If lacerations could be quickly closed with glue, it would be very useful under combat conditions.

TECHNICAL APPROACH

A 6 mm scleral laceration will be created and either left open, closed with Vicryl suture in standard fashion, or closed via application of cyanoacrylate (CA) glue. The animals will be followed clinically by monitoring fundus appearance, intraocular pressure (IOP), intraocular inflammation, and ERG. At 48 hours to 2 months after surgery, the animals are euthanized, and the eyes are examined histopathologically. Wound integrity will be evaluated using Siedel testing while increasing the IOP. An transcleral cannula will be connected to both a transducer and a bag of sterile saline. IOP will be elevated by inflating a sphygnomonometer wrapped around the saline or by digital message of the globe.

PRIOR AND CURRENT PROGRESS

On histopathologic examination, a fibrous bridge was noted in all animals by 2 weeks. Prior to fibrous bridge formation, IOP's and dark-adapted ERG a- and b-wave amplitudes were lower in open eyes compared to those in which wounds were surgically closed using CA or suture. Flare was increased in open eyes. The clinical course of the CA group compared favorably with eyes closed by the standard suture technique. Eyes closed with cyanoacrylate maintained wound integrity while withstanding marked increases in IOP. No animals have been used this fiscal year; 90 have been used for the entire study thus far. There have been no serious and/or unexpected adverse reactions or findings.

CONCLUSIONS

This study supports the efficacy of using cyanoacrylate adhesive as a temporary, battlefield expedient method of closing scleral lacerations.

REPORT DATE: 04/01/93 WORK UNIT # 2320

DETAIL SUMMARY SHEET

TITLE: Mood and Behavior Changes with Topical Ophthalmic Beta-Adrenergic Blockade

KEYWORDS: B-adrenergic, blockers, glaucoma

PRINCIPAL INVESTIGATOR: Blaydon, Sean CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Ophthalmology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if topically administered B-adrenergic blockers have an effect on mood.

TECHNICAL APPROACH
To determine subjective mood by having patients who are being treated with a topical B-blocker (or alternative drug) fill out a periodic questionnaire (Beck Depression Inventory).

PRIOR AND CURRENT PROGRESS
To date, 24 female subjects have been studied (8 this past year), and 31 male subjects have been studied (6 this past year). The study is still proceeding according to the protocol, and recruitment continues. No conclusions have been drawn from the preliminary data. Approximately 15 more males and 15 more females need to be recruited. No serious or unexpected adverse reactions to medications have occurred. Two to three patients have either moved from the area or have been lost to follow-up, and a few patients have had to come off protocol due to failure of randomly assigned medication to control intraocular pressures adequately. The data gathered thus far will be evaluated within the next few months in an attempt to draw some preliminary conclusions.

CONCLUSIONS
None at this time.

REPORT DATE: 07/13/93 WORK UNIT # 2632

DETAIL SUMMARY SHEET

TITLE: Treatment with Liver Transplantation and Human Monoclonal Anti-Hepatitis B Virus IgG of a Hepatitis B Virus Carrier who has End Stage Chronic Active Hepatitis

KEYWORDS: antibody, monoclonal, transplantation

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC
ASSOCIATES: Fernandez, Carlos MD

DEPARTMENT: Department of Surgery
SERVICE: Organ Transplant Service

STATUS: Completed
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the effectiveness of a new human monoclonal anti-hepatitis B virus antibody in the prevention of recurrent hepatitis B infection following liver transplantation in chronic hepatitis B virus carriers with end stage chronic active hepatitis.

TECHNICAL APPROACH

Patients are initially entered into the study at the University of Pittsburgh based on the need for liver transplantation secondary to chronic active hepatitis from hepatitis B virus. Once these conditions have been satisfied, the patient is then presented with the above protocol. They are treated preoperatively with injections of the monoclonal antibody, followed by liver transplantation, and then ongoing treatment postoperatively. This postoperative treatment is continued indefinitely based on the demonstrated half-life of the antibody in each patient. Once this is determined, they are then redosed on an every 2 to 4 week basis.

PRIOR AND CURRENT PROGRESS

A total of two patients have been entered in this study, with no additional patients entered in the last year. In addition, no patients have been entered in the associated study at the University of Pittsburgh Transplantation Institute within the last year. It appears from early investigations in this study that the patients treated with the human monoclonal anti-hepatitis B IGG rapidly developed a mutation within the hepatitis B surface antigen which did not allow binding by this monoclonal antibody. Therefore, no additional patients have been entered into the study, and work has resumed in the in vitro model in an attempt to develop an antibody that would bind with the newly altered hepatitis B surface antigen molecule. No current clinical trials are underway with this human monoclonal antibody.

CONCLUSIONS

At present, the use of this monoclonal antibody appears to be limited in that it apparently induces a change in the target antigen which does not allow binding. Therefore, it is currently not a clinically useable alternative in liver transplantation for the treatment of hepatitis B.

REPORT DATE: 12/14/92 WORK UNIT # 2633

DETAIL SUMMARY SHEET

TITLE: Use of Anti-lymphocyte Preparations in Solid Organ Transplantation

KEYWORDS: anti-lymphocyte, preparations, transplantation

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Organ Transplant Service APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the long-term benefit (1-5 years post transplantation) of anti-lymphocyte preparations used for induction of graft tolerance to prevent rejection episodes, or in the treatment of acute rejection episodes after renal, pancreatic or hepatic transplantation.

TECHNICAL APPROACH
Minnesota antilymphocyte globulin (MALG) will be given daily for the first 10 postoperative days and every other day for 10 days for a total of 15 doses. This will be given to high immunologic risk patients: a) >20% PRA, b) previously transplanted patients, and c) Black recipients. It will also be given to patients with poor initial renal function; i.e., oliguria <200 cc in the first 6 hours, patients who do not respond to IV diuretics with 100 cc/hour output, and patients whose serum creatinine does not fall >2 mg/dl in the first 24 hours post transplant.

PRIOR AND CURRENT PROGRESS
Thirteen patients have been added to the study, for a total of 31 patients who have received ALG prophylactically post transplant. Twenty-six continue to have functioning allografts (84%). The 1 year actuar[illegible] survival rate in this group is 83.6%. This compares favorably to the two prior ALG protocols at this institution: 1) 1980-83, 71% and 2) 1984-89, 85%. Eleven of the 31 patients had transient fevers with initial therapy. Two of the five graft losses were due to rejection which could not be controlled with therapy, and the others were lost to (1) Candida infection, (2) recurrent disease in the renal allograft, and (3) a severe immunologic reaction which is being evaluated as a possible reaction to MALG.

CONCLUSIONS
Prophylactic ALG in this institution is effective in inducing immunologic unresponsiveness following renal transplantation with minimal adverse reactions. Only 6 of 31 recipients had rejection episodes. The rejection rate is 0.23 episodes per patient. This compares favorably to the previous prophylactic ALG protocols: 1) 1980-83, 1.75 episodes per pateint and 2) 1984-89, 0.78 episodes per patient.

REPORT DATE: 12/22/92 WORK UNIT # 2410

DETAIL SUMMARY SHEET

TITLE: The Use of Arthroscopic Abrasion Chondroplasty in the Treatment of Osteoarthritis of the Knee

KEYWORDS: arthroscopic, chondroplasty, osteoarthritis

PRINCIPAL INVESTIGATOR: Hopkinson, William LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 8,439 Total: $ 8,439

STUDY OBJECTIVE
To evaluate the results of abrasion chondroplasty as a treatment for osteoarthritis of the knee.

TECHNICAL APPROACH
Forty patients with osteoarthritis of the knee will be randomized into two treatment groups. One group will have arthroscopy and knee debridement; the other group will have arthroscopy, knee debridement, and abrasion chondroplasty. Annual knee rating, clinical exam, and radiographs will be performed.

PRIOR AND CURRENT PROGRESS
Over the last 5 years, only two patients could be recruited into this study; none this past year. Many patients were interested but did not want to be randomized. Both patients completed the study with full follow-up and had good results with no adverse effects.

CONCLUSIONS
Due to the few patients in the study, the study should be closed.

REPORT DATE: 09/02/93 WORK UNIT # 2417

DETAIL SUMMARY SHEET

TITLE: A Prospective Study of Back Pain in Pregnancy

KEYWORDS: back pain, pregnancy

PRINCIPAL INVESTIGATOR: McHale, Kathleen MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the natural history of back pain in pregnancy and the occurrence and amount of back pain as it relates to weight gain.

TECHNICAL APPROACH
The explanation of the study and the consent form are given to the prenatal patients at the introductory visit. The questionnaire regarding back symptoms and an orthopaedic physical exam are done along with the obstetric exam once during the first, second, and third trimesters, and then at the first post partum check. If the patient continues to have pain at the post partum exam (6 weeks post partum), then the patient continues to be seen by the Orthopaedic Surgery Service until there is some resolution.

PRIOR AND CURRENT PROGRESS
To date, 43 patients have been entered into the protocol (10% of the original goal). No new patients have been entered this past year because of lack of personnel to initiate the interview process. Nonetheless, patient interest in completing this study has been high. This is a minimal risk study; no serious or unexpected adverse reactions have been noted.

CONCLUSIONS
No prospective studies have been published to date evaluating the relationship between back pain and pregnancy. New interest is being shown in the retrospective literature.

REPORT DATE: 10/06/92 WORK UNIT # 2418

DETAIL SUMMARY SHEET

TITLE: Clinical Investigation of the PWB Spine System

KEYWORDS: PWB spine system, spinal fusion

PRINCIPAL INVESTIGATOR: Polly, David Jr MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate a new pedicle fixation device which is more flexible than previously used rigid devices. It is hypothesized that lumbar and lumbosacral fusion rates will be enhanced.

TECHNICAL APPROACH

This is a multicenter study. All patients to be enrolled are candidates for lumbar or lumbosacral fusions with pedicle fixation. There has been no change in the original protocol. Patients will be followed for 4-years post-procedure.

PRIOR AND CURRENT PROGRESS

Due to a high rate of pseudoarthroses with this device, the surgeon stopped implantation at this center in August 1991. Twenty-four patients were entered into the study during this time; 11 have had their PWB instrumentation removed. Nine patients had a pseudoarthrosis, and two had pain over the hardware and a solid fusion on operation. The study center has reached the targeted number of candidates in each category. All study entries have stopped, and the implants were returned to the company. Follow-up visits will continue at specified intervals for the 4-year duration of the study.

CONCLUSIONS

The PWB device allows for too much micromotion at the site, and therefore, fusion does not occur as often.

REPORT DATE: 12/17/92 WORK UNIT # 2419

DETAIL SUMMARY SHEET

TITLE: The Treatment of Carpal Tunnel Syndrome with Pyridoxine

KEYWORDS: carpal tunnel, pyridoxine, vitamin B6

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC
ASSOCIATES: Bagg, Mark MAJ MC; Wynder, Stephen LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define the efficacy of pyridoxine in treatment of carpal tunnel syndrome.

TECHNICAL APPROACH
Prospective randomized study of patients with documented carpal tunnel syndome; patients treated with conservative measures versus those treated with conservative measures plus pyridoxine.

PRIOR AND CURRENT PROGRESS
No patients have been entered into the study at this time. The researchers plan to begin data collection January 1993. Effective FY-93 a new principal investigator, CPT John Xenos, has assumed responsibility for this protocol.

CONCLUSIONS
None.

REPORT DATE: 04/07/93 WORK UNIT # 2420

DETAIL SUMMARY SHEET

TITLE: MRI Characteristics following Surgical Excision of Soft Tissue Sarcomas and Radiation Therapy in Determining Normal Postsurgical and Radiation Changes from Recurrent Disease

KEYWORDS: MRI, soft tissue sarcoma, recurrent disease

PRINCIPAL INVESTIGATOR: Temple, Thomas MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine what the signal characteristics and differences are between post irradiation changes and recurrences in soft tissue sarcomas of the extremities.

TECHNICAL APPROACH
A retrospective chart review will be made of MRI patients who have undergone surgery and radiation therapy for soft tissue sarcomas of the extremities.

PRIOR AND CURRENT PROGRESS
There have been no subjects enrolled in this study. Because of changes in personnel, little substantial progress has occurred in the past year. A new initiative has occurred to reinvigorate this important project. Discussion with Dr. Yvonne Anderjeski, Radiation Oncology, and Dr. Mike Mulligan, Diagnostic Radiology, have reemphasized the need to complete this project. Case lits of possible patients for inclusion have been screened. All pertinent MRI's will be reviewed.

CONCLUSIONS
The result of this study will be important for defining distinctive qualities in postoperative and post-radiation magnetic resonance imaging.

REPORT DATE: 01/07/93 WORK UNIT # 2426

DETAIL SUMMARY SHEET

TITLE: Chart Review of Infected Diabetic Feet

KEYWORDS: diabetic patients, foot ulcerations

PRINCIPAL INVESTIGATOR: Busey, James CPT MS

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review charts for the effect of possible release of endogenous cytokines during local infection to heal diabetic ulcers; and to review diabetic admissions for foot infections and compare diagnostic procedures, treatment, and patient status.

TECHNICAL APPROACH
Diabetic patients with foot ulcerations will be recruited for study and evaluation of wound size, redness, and drainage; both pre- and post-admission. Charts of patients with diabetic ulcers and infections from the Dysvascular Foot Clinic, as well as inpatient records from Internal Medicine, Surgery, and Orthopaedics will be reviewed.

PRIOR AND CURRENT PROGRESS
The medical and surgical treatment records of 23 diabetics admitted with foot infections between August 1987 and January 1991 were reviewed. A manuscript was completed in May 1992, and has been submitted to Southern Medical Journal.

CONCLUSIONS
Diabetic foot cellulitis with no acute ischemic gangrene or systemic sepsis was not a cause for amputation in patients treated after 1987. Radionuclear scans did not influence in-hospital treatment or short-term outcome. Long-term results were not evaluated in these patients.

REPORT DATE: 03/22/93 WORK UNIT # 2427

DETAIL SUMMARY SHEET

TITLE: The Effects of Intraoperative Blood Loss on Serum Antibiotic Level in Patients Undergoing Total Joint Arthroplasty

KEYWORDS: total joint arthroplasty, serum antibiotic levels, blood loss

PRINCIPAL INVESTIGATOR: Hopkinson, William COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 278 Previous FYs: $ 0 Total: $ 278

STUDY OBJECTIVE
To determine what effect blood loss during surgery has on the serum concentration of the antibiotic.

TECHNICAL APPROACH
At least 48 hours preoperatively, the patient will be given 1 gm Cefazolin IV over 5 minutes. Blood samples will be drawn at 5, 10, 20, 30, 60, 120, 240, and 300 minutes. Intraoperatively, the same procedures will be performed, and EBL and intake will be recorded. The serum concentration of the antibiotic in each sample will be determined by capillary electropheresis. The preoperative and intraoperative serum concentrations are compared, and the data is interpreted by the pharmacokineticist.

PRIOR AND CURRENT PROGRESS
One hundred and twenty-seven subjects have been enrolled in this study to date; 12 during this past year. There have been no serious or unexpected adverse reactions, and no patient has withdrawn from the study. The blood loss has ranged from 600-2400 cc. Preliminary analysis has not shown any significant differences between the preoperative serum Cefazolin levels and the intraoperative serum Cefazolin levels. The pharmacokineticist suggests that no more subjects be entered into the study since there has been no clinical or significant difference utilizing this model. One data set needs to be completed by the DCI Support Lab, and a more in-depth analysis will be done.

CONCLUSIONS
In patients undergoing total hip arthroplasty with Cefazolin prophylaxis, no significant decrease in serum concentration of Cefazolin is noted with a blood loss of 600-2400 cc.

REPORT DATE: 10/23/92 WORK UNIT # 2432

DETAIL SUMMARY SHEET

TITLE: Evaluation of the Syndesmosis in Ankle Diastasis Injuries

KEYWORDS: ankle, ligaments, syndemosis

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC
ASSOCIATES: Hopkinson, William COL MC; Olson, Eric MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 2,636 Previous FYs: $ 0 Total: $ 2,636

STUDY OBJECTIVE

To evaluate the role of the syndesmotic ligaments when the ankle is exposed to external rotational forces; to evaluate methods of fixation of the syndesmosis; and to evaluate methods of radiographic assessment of syndesmosis injury.

TECHNICAL APPROACH

Fresh frozen cadaver specimens will be used to study subjects. A special apparatus which allows rotational forces to be applied to the ankle was constructed. The ligaments will be incrementally sectioned, and measurements will be made directly on the specimens while radiographs are made at each incremental cut. The radiographs will be read by three independent observers. An addendum is being considered to evaluate the role of the syndesmotic ligaments when the ankle is exposed to internal rotational forces.

PRIOR AND CURRENT PROGRESS

Thirty-three fresh frozen cadavers have been used. This includes four specimens used in a pilot study to perfect technique and determine the merits of the study.

CONCLUSIONS

Ligamentous injury is related to degree of diastasis and rotation. Partial rupture of the syndesmosis allowed significant diastatis. Suture repair alone is inadequate to resist expected rotational forces. Two screws provide more superior fixation than one screw. The stress lateral radiograph has much better correlation with anatomic diastasis than the stress mortise view.

REPORT DATE: 10/27/93 WORK UNIT # 2433

DETAIL SUMMARY SHEET

TITLE: Foot and Ankle Injuries During Operation Desert Storm/Shield: An Analysis

KEYWORDS: foot and ankle, injuries, warfare

PRINCIPAL INVESTIGATOR: Hayda, Roman CPT MC
ASSOCIATES: HcHale, Kathleen LTC MC; Lower, Raymond DO

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To analyze open injuries to the foot and ankle in modern warfare, with respect to mechanism, extent of soft tissue and bony injury, treatment complications, and outcome at 1 year, in order to establish diagnostic and treatment guidelines.

TECHNICAL APPROACH

The charts of all servicemen treated by the WRAMC Orthopaedic Surgery Service as a result of Desert Storm and Desert Shield will be reviewed. The charts of those who has sustained injuries to the foot and ankle will be reviewed for mechanism of injury, extent of injury to the foot and ankle, associated injury, and treatment. Those with open injuries will be subsequently contacted 12-18 months post injury. A questionnaire and clinical examination will be carried out when possible. The results will be reviewed using the criteria listed above.

PRIOR AND CURRENT PROGRESS

Forty-three of 181 patients from Desert Storm and Shield treated by the Orthopaedic Surgery Service had sustained injuries to the foot and ankle. Of the 43, 60% had open injuries, with 54% of the injuries caused by mines of various types. Follow-up with the telephone questionnaire has been completed on 81% of patients with open injuries.

CONCLUSIONS

War time injury to the foot caused by close proximity blasts results in a severe injury to bony and soft tissue elements. Early treatment with emphasis on debridement (particularly therapy) with early return to functional use, when feasible, will optimize results.

REPORT DATE: 03/29/93 WORK UNIT # 2434

DETAIL SUMMARY SHEET

TITLE: Aggressive Osteolysis Behind Well-fixed Acetabular Components with Perforations

KEYWORDS: hip, adult, arthroplasty

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC
ASSOCIATES: Hopkinson, William LTC(P) MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate cases of uncemented total hip arthroplasty where radiographic evidence of acetabular component loosening or osteolysis is noted. Only acetabular components with perforations will be included.

TECHNICAL APPROACH

This is a retrospective review of cases performed at Walter Reed and at the Anderson Clinic in Virginia. Cases are reviewed and specimens are obtained at hip revision arthroplasty. Specimens are reviewed at AFIP, and retrieved components are evaluated for explanations for failure or increased component wear.

PRIOR AND CURRENT PROGRESS

At this time, three cases have been reviewed and had evaluations completed, while one additional patient awaits revision surgery. There has been evidence of a histiocytic giant cell response at each of the areas of osteolysis, with sheets of polyethylene debris intermixed both intra- and extracellularly.

CONCLUSIONS

This is a descriptive study designed to report specific cases of osteolysis in uncemented acetabular components with perforations in the metal backing. In all of the cases, polyethylene wear debris was found in the areas of lysis. The findings, as well as the histologic analysis, lend support to the current theory that lysis and polyethylene wear debris are related.

REPORT DATE: 04/28/93 WORK UNIT # 2435

DETAIL SUMMARY SHEET

TITLE: The Effect of Extracorporeal Shockwaves on Bone and Soft Tissue in Rabbits

KEYWORDS: shockwaves, dose, response

PRINCIPAL INVESTIGATOR: Brown, Maurice CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To (1) Evaluate ESW's ability to fracture intact bone and determine the accuracy with which such fractures can be created; (2) assess the affect of ESW on soft tissue, as measured by severity of petechiae, ecchymosis, and skin ulceration; (3) examine the dose-response relationship between power delivered and bone and soft tissue injury; and (4) attempt to locate a region of response associated with maximum bone injury and minimum soft tissue injury.

TECHNICAL APPROACH
Power settings of 6, 12, and 19 (6 = 0.42 mJ/mm^, 12 = 0.78 mJ/mm^, 19 = 1.20 mJ/mm^) will be used, and shockwaves will be administered in salvos of 400, 800, or 1200 waves. Animals will be euthanized at 1, 10, and 28 days or whenever a fracture is noted. Petechiae, echymosis, and ulceration will be measured post treatment and at euthanasia. Radiographs will be taken following shockwave application, at the time of euthanasia, or if a fracture is suspected on the basis of clinical evaluation.

PRIOR AND CURRENT PROGRESS
Fifty-four rabbits were treated. Soft tissue changes were more pronounced as power setting and number of shockwaves administered increased. However, a significant finding was that both soft tissue injury and bone affected seemed more dependent upon the power setting than the number of shockwaves administered. The bone/soft tissue affect ratio was greatest when a high power level was used with a lower number of shockwaves. Specimens are currently undergoing histological analysis. These results will be reported in a future study.

CONCLUSIONS
The ability to fracture bone in vivo using ESW has been demonstrated. Soft tissue changes and radiographic affects on bone are described. The dose response data will be useful in future in vitro and in vivo studies and in formulating treatment approaches in clinical trials.

REPORT DATE: 08/10/93 WORK UNIT # 2436

DETAIL SUMMARY SHEET

TITLE: Evaluation of Bone Healing in Osteotomies Produced with Excimer Laser and Er:YAG Laser in the Rabbit Model

KEYWORDS: laser, osteotomy

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopedics Surgery Service APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the ability of excimer laser to effectively ablate bone in vivo; to compare zones of adjacent tissue damage in osteotomies performed using excimer laser and Er:YAG (erbium yttrium-aluminum-garnet) laser; and, to compare healing rates of bone in osteotomies performed using excimer laser to those using Er:YAG laser.

TECHNICAL APPROACH
Sterile surgical techniques will be used under controlled conditions with the following procedures performed on each specimen. All skin incisions will be made using a scalpel blade. On one side, each rabbit will undergo either 'cold' osteotomy to the rib using an oscillating saw, osteotomy with excimer laser, or osteotomy with Er:YAG. On the contralateral side, osteotomy will be performed using either excimer or Er:YAG laser.

PRIOR AND CURRENT PROGRESS
This study has not started yet due to the unavailability of working space and equipment.

CONCLUSIONS
This study will commence in the next several months as the necessary lasers become available.

REPORT DATE: 08/13/93 WORK UNIT # 2522

DETAIL SUMMARY SHEET

TITLE: Vocal Cord Function and Voice Quality Evaluation of Active Duty U.S. Army Drill Instructors

KEYWORDS: videostroboscopy, hoarseness

PRINCIPAL INVESTIGATOR: Paffrath, Jeffrey CPT MC
ASSOCIATES: Patow, Carl CPT MC; McClean, Michael PhD

DEPARTMENT: Department of Surgery
SERVICE: Otolaryngology-Head & Neck Service

STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To prospectively document the laryngeal pathology and describe the acoustic effects of voice abuse in active duty U.S. Army drill instructors.

TECHNICAL APPROACH

State-of-the-art videostroboscopic techniques and a computerized speech lab will be used to accurately assess the vocal pathology of drill instructors during the first week of intense field training. The information gained through this study could form a basis for future treatment modalities.

PRIOR AND CURRENT PROGRESS

Funding for this protocol has been requested from the U.S. Army Medical Research and Development Command. At the time of this report, year-end monies have been offered if obligation of the funds can be completed by the end of the fiscal year. Hopefully, this will be possible.

CONCLUSIONS

Study of subjects has not been possible to date.

REPORT DATE: 10/13/93 WORK UNIT # 2523

DETAIL SUMMARY SHEET

TITLE: Reliability of High-Frequency Thresholds in Normal and Hearing-Impaired Subjects

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hansen, Karla CPT MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Otolaryngology-Head & Neck Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 03/10/93 WORK UNIT # 2501

DETAIL SUMMARY SHEET

TITLE: Tensile Strength of Wounds Closed Under Increasing Tension in the Pig Model

KEYWORDS: wound closing tension, scar tensile strength, positive relationship

PRINCIPAL INVESTIGATOR: Livermore, George CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Otolaryngology-Head & Neck Surgery Svc APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 5,874 Total: $ 5,874

STUDY OBJECTIVE

To assess the relationship between wound closing tension and scar tensile strength in the pig animal model. A positive relationship has previously been shown in the rat model.

TECHNICAL APPROACH

Ten Hampshire pigs will be subjected to skin excisional wounds of varying degrees. The scars will be harvested at 30 days postop and sent for analysis of tensile strength, histology, and biochemical analysis. The findings will be compared for statistically significant relationships.

PRIOR AND CURRENT PROGRESS

This project was completed with the last report. Data analysis has been completed as well. A manuscript is in preparation and should be submitted for publication during the upcoming fiscal year

CONCLUSIONS

The relationship between wound closing tension and scar tensile strength observed in the rat has been repeated in the pig. At higher tensions, the relationship is non-linear.

REPORT DATE: 05/26/93 WORK UNIT # 2503

DETAIL SUMMARY SHEET

TITLE: Salicylate Ototoxicity in Humans, A Clinical Study

KEYWORDS: salicylate, aspirin, audiometric testing

PRINCIPAL INVESTIGATOR: Stambaugh, Kweon LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Otolaryngology-Head & Neck Surgery Svc APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the otologic effect of salicylate (specifically aspirin) in humans with conventional and high frequency audiometry with serum salicylate level correlation.

TECHNICAL APPROACH
Subjects will be accrued and undergo audiometric testing with no salicylate on board for baseline determination. Thereafter, five varying clinical dosage levels of ASA trials, by daily ingestion for a week, will be undertaken with audiometry at the end of each week. A week of rest off ASA will be given to each volunteer participant to allow return to baseline audiometric levels. Data will be collected and correlated with serum levels of ASA taken prior to each audiometric test.

PRIOR AND CURRENT PROGRESS
This study was never initiated and has been ongoing since May 1990. The study appears to have been delayed, in part, by a logistical holdup in purchasing the audiometer. Additionally, the original principal investigator has departed this center.

CONCLUSIONS
This study will probably be reinitiated after an appropriate principal investigator has been recruited.

REPORT DATE: 06/28/93 WORK UNIT # 2517

DETAIL SUMMARY SHEET

TITLE: Hemostatic Assessment of the Preoperative Tonsillectomy Patient

KEYWORDS: adenotonsillectomy, bleeding

PRINCIPAL INVESTIGATOR: Close, Heidi CPT MC
ASSOCIATES: Alving, Barbara COL MC; Kryzer, Thomas MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Otolaryngology-Head & Neck Surgery Servi APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine a preoperative hemostatic assessment for adenotonsillectomy patients that is valuable in predicting bleeding risk. Specifically, to determine if general screening coagulation studies are a valuable contribution to a bleeding questionnaire and physical exam.

TECHNICAL APPROACH
Patients will complete a physical exam and bleeding questionnaire, and general coagulation studies will be submitted to WRAMC laboratory. Perioperative bleeding complications will be assessed and correlated with preop evaluation. A modification includes sending two blue-top samples to WRAIR at the same time as blood is drawn in the WRAMC laboratory. This allows evaluation of an abnormal preop assessment to proceed without the patient returning for an additional venipuncture.

PRIOR AND CURRENT PROGRESS
A case series of 114 patients undergoing tonsillectomy alone or tonsillectomy and adenoidectomy, 96 of whom completed questionnaires and screening laboratory studies, were enrolled in this study. Of the 96 patients completing the questionnaire, 21 gave a positive response to questions concerning easy bruisability, menorrhagia, epistaxis, or family history of bleeding. A total of 18 patients had one of the following abnormalities: prolonged APTT (N=16), prolonged PT (N=1), or decrease in platelet count (N=1). None of the laboratory abnormalities were hemostatically significant. Of the six patients showing evidence of bleeding in the postoperative period, none had an abnormal laboratory value, and none gave any positive responses on the questionnaire.

CONCLUSIONS
Hemostatic problems that occur in patients undergoing tonsillectomy were not predicted by routine screening studies or even by positive responses to a questionnaire. The data suggest that laboratory evaluation of hemostasis should not be performed unless the response to a questionnaire concerning hemostasis suggests a bleeding disorder.

REPORT DATE: 09/03/93 WORK UNIT # 2115

DETAIL SUMMARY SHEET

TITLE: Primary Varicose Veins: Quantification of Physiologic Changes After Treatment

KEYWORDS:

PRINCIPAL INVESTIGATOR: Cabellon, Silverio COL MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Peripheral Vascular Surgery Service APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This protocol was administratively terminated.

TECHNICAL APPROACH
This protocol was administratively terminated.

PRIOR AND CURRENT PROGRESS
None. This protocol was administratively terminated.

CONCLUSIONS
This protocol was administratively terminated.

REPORT DATE: 10/15/92 WORK UNIT # 2910

DETAIL SUMMARY SHEET

TITLE: The Use of Bone Repair Materials for Maxillary Alveolar Clefts

KEYWORDS: bone, repair, materials

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the standard of care for bone regeneration, the autogenous bone graft, to experimental materials consisting of a biodegradable carrier and a bone inductive protein (BIP).

TECHNICAL APPROACH

The model for this comparison will be maxillary alveolar clefts in dogs. Initially, the alveolar clefts will be created along with an oronasal fistula lined with epithelium. Six dogs each will be randomized into four treatment groups: untreated control, autologous bone graft, biodegradable carrier, and biodegradable carrier with BIP. Four months after the clefts are treated, the recipient beds, including the experimental materials, will be recovered and evaluated by quantitative microscopy and histology.

PRIOR AND CURRENT PROGRESS

A total of 26 dogs have been used for this study. As mentioned in the previous annual report, two animals were euthanized at the recommendation of the veterinarian (MAJ Greenfield) due to non-related causes. The necropsy reports were finally obtained, and the canines were replaced. This past year, the alveolar clefts were randomly treated with four treatment modalities: autogenous iliac bone, biodegradable carrier, biodegradable carrier + recombinant BIP (bone inductive protein), and the control. These were allowed to mature, and the canines (24) were euthanized and the maxillae harvested. The specimens were sent to the Harrington Arthritis Research Center for histological slide preparation. Photographs and radiographs were obtained from the specimens.

CONCLUSIONS

The histological slide preparations have not been received. Review of the radiographs reveals somewhat equivocal results with the carrier + BP. Final results will await the histomorphometric analysis.

REPORT DATE: 10/15/92 WORK UNIT # 2911

DETAIL SUMMARY SHEET

TITLE: Orbital Floor Reconstruction with Bone Repair Materials

KEYWORDS: bone, repair, materials

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the use of resorbable PLA:PGA plus a bone inductive protein (BIP) with PLA:PGA alone and with controls of operated but non-reconstructed animals in the surgical reconstruction of the orbital wall and orbital floor defects.

TECHNICAL APPROACH

The model will be orbital wall/floor defects in the non-human primate species (NHPS) (Macaca mulatta). Initially, the orbital floor/wall defects will be created and repaired with a biodegradable carrier or biodegradable carrier plus BIP. The three treatment groups will consist of the biodegradable carrier, the carrier plus BIP, or the untreated defect. Eighteen NHPS will be utilized. Three months post-treatment, the specimens and experimental materials will be retrieved and evaluated by quantitative microscopy and histology.

PRIOR AND CURRENT PROGRESS

Due to the lack of highly purified BIP and lack of facilities/non-human primates, the project could not be completed this fiscal year.

CONCLUSIONS

Awaiting initiation of the protocol.

REPORT DATE: 10/15/92 WORK UNIT # 2912

DETAIL SUMMARY SHEET

TITLE: Rigid Skeletal Fixation of the Immature Craniofacial Skeleton

KEYWORDS: rigid, skeletal, fixation

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC; Bley, Jack MAJ VC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effects of rigid skeletal fixation on skull growth and bone repair in both osteotomized and non-osteotomized immature non-human primate species calvaria.

TECHNICAL APPROACH
Through a coronal approach, a frontal bone flap and supraorbital bar will be created and either fixed in place or advanced with either semi-rigid fixation (wire fixation) or rigid fixation (plates and screws). The fifth treatment group will consist of the control. At 6 months, three non-human primate species from each treatment group will be euthanized and the skulls evaluated using topographical landmarks and a three SPACE digitizer. The cranial module will be calculated for each specimen. Individual cranial metric measurements will be divided by the individual cranial modules. The remainder of the non-human primate species will be euthanized at 1 year post-treatment, and the skulls evaluated similarly.

PRIOR AND CURRENT PROGRESS
Due to problems locating a vendor which could supply the number of immature non-human primates (virus-free) required, problems with contracting which almost prevented obtaining the monkeys at the correct age, and the need for quarantine after delivery, only two monkeys have undergone surgery. The frontal bone flap and supraorbital bar were created. One was fixed in place in the normal anatomic position with titanium plates and screws, and the other was advanced 7 mm prior to rigid fixation. Ten additional non-human primates have been received, undergone quarantine, and are awaiting surgery.

CONCLUSIONS
No preliminary conclusions can be drawn at this time.

REPORT DATE: 03/12/93 WORK UNIT # 2913

DETAIL SUMMARY SHEET

TITLE: Platelet Derived Growth Factor Formula in the Treatment of Chronic Wounds

KEYWORDS: growth factors, platelets, wound

PRINCIPAL INVESTIGATOR: Antoine, Gregory LTC MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Plastic Surgery Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effect platelet products have on the healing of diabetic chronic ulcers. This project will also serve as a pilot study of non-diabetic wounds.

TECHNICAL APPROACH
This is a double-blind, crossover, control study. Each patient will be treated for 3 weeks with a salve prepared from their own platelets or with a placebo salve. Following a 2 week washout period, there will be a crossover. After completion of the 8 week study, the patients may enter an open study of platelet formulation for no more than 6 weeks. If the wound is unhealed at that time, the patients will be offered WU# 2113 as an alternative.

PRIOR AND CURRENT PROGRESS
This study has been administratively terminated.

CONCLUSIONS
This study has been administratively terminated.

REPORT DATE: 08/02/93 WORK UNIT # 2712

DETAIL SUMMARY SHEET

TITLE: Surgical Implications of Three-dimensional Modeling of the Heart

KEYWORDS: modeling, heart, computer

PRINCIPAL INVESTIGATOR: Edward , Fred COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Thoracic Surgery Service APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To focus on the creation of an accurate detailed extensive two- and three-dimensional computer graphic model of the normal adult human heart and its integration with an interactive computer-aided interface.

TECHNICAL APPROACH
For this project, a Silicon Graphics 4D/310VGX graphics workstation will be utilized. Incorporating a 33 MHz RISc processor, the system will be capable of 30 MIPS and 5 MFLOPS of performance. The VGX graphics subsystem will provide 40 MFLOPS of performance dedicated to graphics processing and 48 bits of color display. This system is capable of real time manipulation of highly complex rendered 3-dimensional objects. Two commercial software packages will be used to provide the maximum number of possible applications for the 3-dimensional cardiothoracic data set.

PRIOR AND CURRENT PROGRESS
This study is being terminated due to recent notification from the U.S. Army Medical Research and Development Command that funding is not available.

CONCLUSIONS
None.

REPORT DATE: 10/05/92 WORK UNIT # 2713

DETAIL SUMMARY SHEET

TITLE: Secondary Prospective Study for the Evaluation of the Safety and Effectiveness of Cryopreserved Human Allograft Heart Valves (LifeNet)

KEYWORDS: cryopreserved human valve, valved allograft conduits

PRINCIPAL INVESTIGATOR: Zurcher, Robert MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Thoracic Surgery Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine via a prospective study the efficacy and side effects of the use of cryopreserved human valves for use in patients.

TECHNICAL APPROACH
Diseased valves will be replaced with human cryopreserved allografts using standard cardiac surgical techniques. Addtionally, valved allograft conduits will be used in children in whom there may be a congenital absence or deficiency of a native valve.

PRIOR AND CURRENT PROGRESS
This is a large multicenter study, and WRAMC has not entered any patients into it since IRB approval. The overall results of the study are unknown.

CONCLUSIONS
No patients have been entered from this institution so no conclusion is yet possible.

REPORT DATE: 10/05/92 WORK UNIT # 2714

DETAIL SUMMARY SHEET

TITLE: Cryovalve Heart Valve Allografts Replacement Heart Valve Allograft (CryoLife)

KEYWORDS: cryopreserved human valve, valved allograft conduits

PRINCIPAL INVESTIGATOR: Zurcher, Robert MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Thoracic Surgery Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
A prospective study to determine the efficacy and side effects of the use of cryopreserved human valves for use in patients.

TECHNICAL APPROACH
Diseased valves will be replaced with human cryopreserved allografts using standard cardiac surgical techniques. Additionally, valved allograft conduits will be used in children in whom there may be a congenital absence or deficiency of a native valve.

PRIOR AND CURRENT PROGRESS
This is a large multicenter study, and WRAMC has not entered any patients into the study since IRB approval. The overall results of the study are not yet known.

CONCLUSIONS
No patients have been entered from this intitution so no conclusion is yet possible.

REPORT DATE: 02/10/93 WORK UNIT # 2837

DETAIL SUMMARY SHEET

TITLE: NPCP 2200 A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate

KEYWORDS: leuprolide, flutamide, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Feb 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To try and determine if the antiandrogen flutamide will increase the efficacy of leuprolide.

TECHNICAL APPROACH
Patients are randomized to receive leuprolide and flutamide or leuprolide and placebo. At the time of progression, the blind is broken, and patients not receiving flutamide will be given the drug.

PRIOR AND CURRENT PROGRESS
This study is a multiple group cooperative effort, and accrual of 600 patients is expected. WRAMC has randomized 24 patients to this protocol; 5 this past year. Two patients are being followed on drug, and three patients are being followed off drug. Eighteen patients have died due to prostate cancer. One patient is lost to follow-up. No new patients will be enrolled in this study; study remains open for follow-up only.

CONCLUSIONS
In patients with advanced prostate cancer, treatment with leuprolide and flutamide is superior to treatment with leuprolide alone.

REPORT DATE: 10/14/92 WORK UNIT # 2843

DETAIL SUMMARY SHEET

TITLE: ECOG EST 1887 A Phase III Trial of Cystectomy Alone Vs. Neoadjuvant M-VAC + Cystectomy in Patients with Locally Advanced Bladder Cancer

KEYWORDS: cisplatin, cystectomy, bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the survival in patients with locally advanced bladder cancer who are treated with cystectomy alone to those who are treated with M-VAC (methotrexate/vinblastine/Adriamycin/cisplatin) followed by cystectomy in a randomized Phase III neoadjuvant trial; and to quantify the "tumor downstaging" effect of neoadjuvant M-VAC.

TECHNICAL APPROACH
This is a randomized, multicenter, Phase III trial for patients with T2-T4a, NO, MO transitional cell carcinoma of the bladder with or without squamous differentiation. Patients are randomized to radical cystectomy or M-VAC plus radical cystectomy.

PRIOR AND CURRENT PROGRESS
A total of 80 patients have been enrolled; two of them WRAMC patients. One of these WRAMC patients, enrolled in 1990, was randomized to M-VAC plus radical cystectomy. This patient is doing very well at the present time. The other WRAMC patient, enrolled in 1991, was randomized to cystectomy only. This patient died of metastatic bladder cancer in May 1992.

CONCLUSIONS
None at this time.

REPORT DATE: 04/27/93 WORK UNIT # 2854

DETAIL SUMMARY SHEET

TITLE: ECOG EST 3886 Randomized Phase III Evaluation of Hormonal Therapy Vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy

KEYWORDS: zoladex, orchiectomy, adenocarcinoma/prostate

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the time to progression and survival in patients with histologically confirmed Stage D1 prostate cancer following radical prostatectomy and pelvic lymphadenectomy treated with no immediate hormonal therapy compared to those treated immediately with hormonal therapy.

TECHNICAL APPROACH
This is a multicenter randomized Phase III trial. Patients can be randomized to hormonal therapy or observation. Those patients randomized to observation may be registered to receive hormonal therapy if their disease progresses. All patients that progress on hormonal therapy will be followed off study drug.

PRIOR AND CURRENT PROGRESS
Altogether, 87 patients (1 from WRAMC) have been enrolled; none this past fiscal year. The one WRAMC patients was randomized to the hormone therapy (Zoladex). This patient is doing well and has experienced no adverse reactions to therapy. This study has been closed due to poor accrual, effective 17 March 1993. Patients will be followed according to protocol.

CONCLUSIONS
None at this time.

REPORT DATE: 09/15/93 WORK UNIT # 2859

DETAIL SUMMARY SHEET

TITLE: SWOG 8894 A Comparison of Bilateral Orchiectomy with or without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer

KEYWORDS: cancer, prostate, orchiectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test the hypothesis that total androgen blockade (orchiectomy plus flutamide) may be better than orchiectomy alone.

TECHNICAL APPROACH
This is a prospective, randomized, double-blind, placebo-controlled study.

PRIOR AND CURRENT PROGRESS
To date, 32 patients have been randomized to this protocol; 4 during this past year. There have been no serious or unexpected adverse reactions related to the therapy. Fifteen patients have died due to prostate cancer. The 17 remaining patients are being followed in the Urology Clinic every 3 months or sooner if necessary. Seven are being followed on the study drug (flutamide vs. placebo), seven are being followed off drug, and three are being followed on open-labeled flutamide.

CONCLUSIONS
None at this time.

REPORT DATE: 10/14/92 WORK UNIT # 2860

DETAIL SUMMARY SHEET

TITLE: Expression of C-ErbB-2 Oncoprotein in Prostatic Carcinoma

KEYWORDS: c-ErbB-2, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Kuhn, Eric MAJ MC; Sesterhenn, Isabel MD

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Completed
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 482 Total: $ 482

STUDY OBJECTIVE

To determine if the c-erbB-2 oncogene protein is over expressed in prostate cancer. In breast cancer, this oncogene's expression correlates to adverse prognosis, and we seek to determine if a similar association is present for prostate cancer.

TECHNICAL APPROACH

(1) Obtain paraffin archival pathologic material from prostate cancer cases. (2) Immunohistochemistry staining for c-erbB-2 oncoprotein in sections from these cases. (3) Correlation of staining to clinical outcome. (4) Differential polymerase chain reaction (PCR) to assay for c-erbB-2 gene amplification in those cases that exhibited protein expression.

PRIOR AND CURRENT PROGRESS

The study has been completed with the following findings: (a) Definite positive membranous staining for c-erbB-2 oncoprotein was detected in 18/53 (34%) clinically localized prostatic carcinomas: (b) Staining was essentially equally distributed among grades and stages: 6/27 (22%) well differentiated; 8/20 (40%) moderately differentiated; 4/6 (66%) poorly differentiated; 6/18 (33%) pathologic Stage B; 12/33 (36%) pathologic Stage C; (c) For the 18 positive staining cases, no gene amplification was detected via differential PCR; and (d) at a mean follow-up of 36 months, there was a trend toward a more adverse prognosis for those cases expressing the c-erbB-2 oncoprotein.

CONCLUSIONS

Approximately one-third of clinically localized prostate cancers express the c-erbB-2 oncoprotein via immunohistochemistry using pAB-1 in archival material. Although oncoprotein expression was detected, no cases demonstrated DNA gene amplification. Although results are preliminary, c-erbB-2 might be a prognostic marker for prostate cancer.

REPORT DATE: 04/08/93 WORK UNIT # 2862

DETAIL SUMMARY SHEET

TITLE: Flow Cytometric Proliferative Activity in Stage I Nonseminomatous Testicular Cancer

KEYWORDS: flow cytometry, testicular cancer, Stage I

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Foley, John MAJ MC; Hitchcock, Charles MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Completed
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 13,889 Total: $ 13,889

STUDY OBJECTIVE

To determine if DNA flow cytometric proliferative index (PI) measurement helps aid more accurate staging of clinically localized testicular cancer. To determine if this flow cytometric measurement (FCM) parameter will discern who is pathologic Stage I vs. occult Stage II.

TECHNICAL APPROACH

The cohort consists of all patients treated at Walter Reed since 1980 who were clinical Stage I preoperatively and then underwent retroperitoneal lymphadenectomy for testicular cancer. From this group, two subgroups were identified: Group 1 were patients without retroperitoneal metastases who were pathologic Stage I; group 2 were patients with occult retroperitoneal metastases discovered and, therefore, upstaged to Stage II. Paraffin archival histological material was obtained on these cases and subjected to FCM.

PRIOR AND CURRENT PROGRESS

The study is now completed. A manuscript has been accepted by the Journal of Urology and is in press.

CONCLUSIONS

Flow cytometric proliferative activity was statistically more elevated in Stage II patients; however, multivariate analysis showed that calculation of percentage of embryonal carcinoma in the primary tumor was more significant than flow measurements.

REPORT DATE: 08/02/93 WORK UNIT # 2864

DETAIL SUMMARY SHEET

TITLE: ECOG EST 9887 A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy

KEYWORDS: prostate cancer, pathologic Stage C, adjuvant radiotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 500 Total: $ 500

STUDY OBJECTIVE
To compare in a randomized study, the disease-free survival rates in completely resected patients with pathologic Stage C (T3NOMO) carcinoma of the prostate assigned to be treated with adjuvant external beam radiotherapy to that in patients assigned to receive no adjuvant therapy. To assess the qualitative and quantitative toxicities of patients with pathologic Stage C carcinoma of the prostate when treated with external beam radiotherapy.

TECHNICAL APPROACH
After prostatectomy with pelvic lymphadenectomy and no evidence of regional lymph node or metastatic disease, the patient is randomized to receive adjuvant radiation therapy or no adjuvant therapy. All patients are off treatment 1 year after randomization or at disease progression.

PRIOR AND CURRENT PROGRESS
Four patients have been randomized to this protocol; one since July 1992. Three patients have been randomized to radiation and have done well on their treatments. One was randomized to observation and is doing well. There has been no incidence of unexpected or serious adverse reactions.

CONCLUSIONS
None.

REPORT DATE: 07/12/93 WORK UNIT # 2865

DETAIL SUMMARY SHEET

TITLE: A Randomized Trial of Transurethral Resection of the Prostate Vs. Open Prostatectomy or Nonoperative Treatment

KEYWORDS: prostate, TURP, BTOPS

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen LTC MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether long-term mortality rates vary in men treated for symptomatic benign prostatic hypertrophy (BPH) by non-operative strategies vs operative means; to establish efficacy of non-operative treatment strategies vs TURP for men with symptomatic BPH; and to compare short- and long-term outcomes of TURP vs open prostatectomy for men with symptomatic BPH and large prostate glands.

TECHNICAL APPROACH
This is a multicenter clinical trial randomizing patients on a stratified basis (prostate size, anti-hypertensive, prostate anatomy) to receive either open prostatectomy, transurethral prostatectomy, or non-operative strategies (balloon dilation, alpha blockers, or watchful waiting control arm). Patients are evaluated with an initial symptom score and objective flow parameters and are followed periodically for procedure efficacy and overall mortality. Amendments necessitated by funding constraints have now limited the study to two arms; TURP vs. balloon dilation.

PRIOR AND CURRENT PROGRESS
To date, 73 patients from WRAMC have been enrolled into this protocol: 53 were randomized (5 drug, 9 balloon, 11 watchful waiting, 2 open, and 26 TURP) while 20 subjects were non-randomized (2 drug; 0 balloon, 5 watchful waiting, 2 open, and 11 TURP). During the past year, 12 patients have been enrolled. Groupwide, 174 patients have been randomized and 108 non-randomized (as of January 1993). The protocol has been temporarily closed to enrollment and follow-up of Class II (eligible for open prostatectomy vs. TURP) patients, non-randomized patients, patients randomized to terazosin, patients randomized to Class 1C (not eligible for balloon dilation), and Class 1D (not eligible for either terazosin or balloon dilation). There have been no serious or unexpected adverse reactions during this study. Benefits to study subjects are pending completion of the research protocol.

CONCLUSIONS
No conclusions to date.

REPORT DATE: 09/15/93 WORK UNIT # 2868

DETAIL SUMMARY SHEET

TITLE: Randomized Prospective Study Comparing Radical Prostatectomy Alone Versus Radical Prostatectomy Preceded by Androgen Blockade in Clinical B2 (T2bNxMo) Prostate Cancer

KEYWORDS: androgen blockage, prostate cancer, Stage B2

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the safety and efficacy of a combination of leuprolide and flutamide prior to radical prostatectomy in clinical Stage B2 prostate cancer as compared to no therapy before radical prostatectomy.

TECHNICAL APPROACH
This is a multicenter, randomized study which will compare the safety and efficacy of leuprolide plus flutamide prior to radical prostatectomy to radical prostatectomy alone.

PRIOR AND CURRENT PROGRESS
Twenty-one patients have been enrolled into this protocol. Ten patients have been randomized to receive androgen blockage before surgery. Eleven patients have been randomized to prostatectomy alone. All patients have had surgery and have done well postoperatively. Seven patients were enrolled in 1993. No incidence of serious or unexpected adverse reactions has been reported.

CONCLUSIONS
None as yet.

REPORT DATE: 10/19/92 WORK UNIT # 2869

DETAIL SUMMARY SHEET

TITLE: Response Patterns to DDAVP (Desmopressin Acetate) in the Treatment of Nocturnal Enuresis as a Function of Change in Urine Osmolality

KEYWORDS: nocturnal enuresis, urine osmolality

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen LTC MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the long-term safety and efficacy of DDAVP and response patterns to changes in urine osmolality in patients with primary nocturnal enuresis.

TECHNICAL APPROACH
Patients will be randomized to receive DDAVP placebo after a 2 week baseline period in a double-blind fashion for 4 weeks. They will then receive open label drug for 4 months. During the lead-in and double-blind period, urine osmolalities will be assessed.

PRIOR AND CURRENT PROGRESS
Twelve patients have been randomized. One patient withdrew during the open label study due to ineffectiveness of therapy, and one patient was dropped due to shortness of breath; leaving 10 evaluable patients. Accrual is ongoing. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Pending study conclusion.

REPORT DATE: 11/16/92 WORK UNIT # 2870

DETAIL SUMMARY SHEET

TITLE: ECOG EST 1889: A Study of 5-Fluorouracil and Leucovorin in Metastatic Prostate Cancer

KEYWORDS: prostate cancer, 5-fluorouracil, leucovorin

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the response rate and duration, survival, and toxicity of 5-fluorouracil (5-FU) and leucovorin (LV) in patients with advanced prostate cancer (hormone refractory).

TECHNICAL APPROACH
Those patients identified with advanced prostate cancer will be registered to receive 5-FU (425 mg/m2) and LV (20 mg/m2) for a total of six cycles.

PRIOR AND CURRENT PROGRESS
There have been no patients eligible for randomization into this protocol from WRAMC Urology Clinic. Notification has been received from the ECOG that this study has been closed effective November 4, 1992.

CONCLUSIONS
None at this time.

REPORT DATE: 01/14/93 WORK UNIT # 2871

DETAIL SUMMARY SHEET

TITLE: A Randomized, Comparative Trial of Casodex Versus Flutamide Used in Combination with Medical Castration in Patients with Untreated Metastatic Prostate Cancer

KEYWORDS: casodex, medical castration, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy and safety of casodex versus flutamide used in combination with LHRH analogs, in patients with untreated metastatic prostate cancer according to: time to treatment failure, quality of life, tolerability, subjective response, and survival.

TECHNICAL APPROACH
This is a randomized, comparative, multicenter trial. Patients will be randomized to zoladex implant or leuprolide depot in a 2:1 ratio, and between one of two antiandrogens (casodex or flutamide) in a 1:1 ratio.

PRIOR AND CURRENT PROGRESS
Seven patients have been randomized to this protocol. Five patients are receiving zoladex plus an antiandrogen (casodex or flutamide). Two patients are receiving leuprolide plus an antiandrogen. All patients are doing very well on their assigned treatments. There have been no serious or unexpected adverse reactions

CONCLUSIONS
None at this time.

REPORT DATE: 02/09/93 WORK UNIT # 2872

DETAIL SUMMARY SHEET

TITLE: EOG EST C-0490: Phase II Study of Difluromethylornithine (DFMO) in Patients with Superficial and Superficially-Invasive Bladder Cancer

KEYWORDS: DEMO, bladder, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Abt, Mary Beth RN; McI COL MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the safety and efficacy of oral difluromethylornithine (DEMO) in superficial and superficially invasive cell carcinoma of the urinary bladder.

TECHNICAL APPROACH
Prospective randomized trial of four dose schedules of oral DEMO in patients with pathologically proven Ta No Mo or T1 No Mo transitional cell carcinoma of the bladder. Patients will be monitored every 3 months with labs, cystoscopy, bladder cystologies, and audiograms.

PRIOR AND CURRENT PROGRESS
Four patients have been entered onto the study, and are being followed. Active accrual is still being performed. No patients have discontinued the study because of serious or unexpected adverse reactions.

CONCLUSIONS
The study is in progress, and no conclusions or interim analysis is available at this time.

REPORT DATE: 05/24/93 WORK UNIT # 9802

DETAIL SUMMARY SHEET

TITLE: Production of Positive and Negative Control Slides and Mouse Brain Suspension for Fluorescent Rabies Antibody Test

KEYWORDS: rabies

PRINCIPAL INVESTIGATOR: Mouer, Thomas DAC

SERVICE: Veterinary Services STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To produce positive and negative control slides and absorbing suspensions for specific rabies antigen identification.

TECHNICAL APPROACH
Suspensions of normal and rabies infected mouse brains will be used to identify rabies antigen in suspect brain tissue. Fluorescein labelled anti-rabies globulin will be used for all positive, negative, and suspect tissue.

PRIOR AND CURRENT PROGRESS
There has been no progress this past year. The laboratory is being closed.

CONCLUSIONS
None.